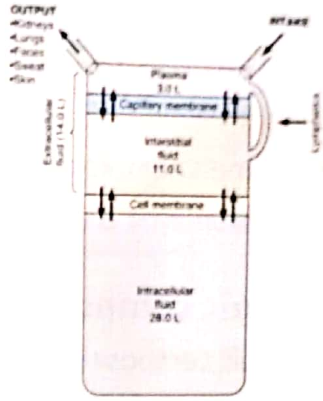
Daily intake of water:

- Ingested form of liquid is 2100 ml/day.
- Liquid synthesized by oxidation is 200 ml/day.
- Total water intake is 2300 ml/day.

Daily loss of water from body:

- Insensible water loss through skin is 300-400 ml/day. Burns increase evaporation. So persons with burns must be given large amounts of fluid.
- Insensible water loss through respiratory tract is 300-400 ml/day.
- In cold weather greater loss of water occurs from lungs.
- Water loss in sweat is 100 ml/day.
- Water loss in feces is 100 ml/day.
- Water loss in urine is 1-1.5 L/day.



Body fluid regulation

Body Fluid compartments:

- All transcellular fluids (synovial, peritoneal, pericardial, intraocular fluids and CSF) constitute about 1-2 liters.
- In a 70 kg man total body water is 60% of body weight or about 42 liters.
- As a person grows older, percentage of total body weight that is fluid gradually decreases b/c total body water is inversely proportional to body fat. Aging is associated with an increase in body fat percentage by weight.
- In women total body water average about 50% of body weight b/c women have a greater percentage of body fat.
- In premature and newborn babies total body water ranges from 70-75% of body weight.

Intercellular Fluid Compartments:

- 28 liter of intracellular fluid constitutes about 40% of total body weight.

Extracellular Fluid Compartments:

- 14 liter of extracellular fluid constitutes about 20% of total body weight.
- Interstitial fluid makes up more than three fourths (11 liters) of extracellular fluid.
- Plasma makes up almost one-fourth of extracellular fluid or about 3 liter.
- Plasma is the non-cellular part of bold.
- Plasma and interstitial fluid have about same composition except for proteins, which have a higher concentration in plasma.

Fluid	**Volume** (Liters)	**Percentage of**	
		Body fluid	**Body weight**
TBW	42	100 %	60 %
ICF	28	67 %	40 %
ECF	14	33 %	20 %
ISF	11	25 %	15 %
IVF Blood (plasma)	3	8 %	5 %

Body fluid Compartments

Blood volume:

- Blood contains both extracellular fluid (plasma) and intracellular fluid (fluid in RBCS).
- Average blood volume of adults is about 7% of body weight or about 5 liters.
- About 60% of blood is plasma and 40% is red blood cells.

Hematocrit:

- It is fraction of the blood composed of red blood cells.
- In men hematocrit is about 0.40.
- In women it is about 0.36.

Ionic composition of plasma and interstitial fluid:

- Ionic composition of plasma and interstitial fluid is same b/c of donnan effect the concentration of cations is slightly greater (2%) in plasma than in the interstitial fluid. The plasma has a net negative charge and therefore tends to bind cations such as sodium an potassium.
- Negatively charred ions (onions) tend to have higher concentration in interstitial fluid compared with plasma b/c negative charges of plasma proteins repel negatively charge onions.

Donnan Effect:

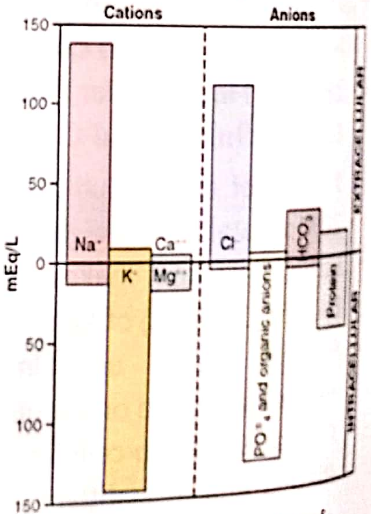
- Phenomenon of predictable and unequal distribution of permeant charged ions on eithe side of a semipermeable membrane, in the presence of impermeant charged ions.

Permeant Ions:

- Ions that can pass through a semipermeable membrane.

Constituents of Extracellular fluid:

- Major cation of extracellular fluid is sodium.
- Major anions of extracellular fluid are chloride and bicarbonate ions.



Major cations and anions of Body fluid Compartments

Constituents of Intracellular Fluid:

- Major cations of intracellular fluid are potassium and magnesium ions.
- Major anions of intracellular fluid are protein and phosphate ions.
- Cells contain large amounts of protein almost four times as much as in the plasma.
- Intracellular fluid has no calcium ions.

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Nonelectrolytes of Plasma:

Phospholipid;	280 mg/dl
Cholesterol;	150 mg/dl
Glucose;	90 mg/dl
Urea;	14 mg/dl
Lactic acid;	10 mg/dl
uric acid	3 mg/dl
Creatinine	1 mg/dl
bilirubin	0.5 mg/dl

Electrolytes in extracellular and intracellular fluid:

Electrolytes	Extracellular Fluid (mOsm/L H_2O)	Intracellular Fluid (mOsm/L H_2O)
Na^+	142	14
K^+	4.2	140
C_a^{++}	1.3	0
Mg^{++}	0.8	20
Cl^-	108	4
HCO_3^-	24	10

The indicator dilution principle:

- The volume of a fluid compartment in the body can be measured by using "the indicator dilution principle".
- This method is based on the conservation of mass principle, which means that the total mass of a substance after dispersion in the fluid compartment will be the same as the total mass in injected into the fluid compartment.

Formula used as, Volume = Amount of substance present/concentration in plasma

Determination of volumes of specific body fluid compartments:

Measurement of total body water:

- Radioactive water (tritium, $3H_2O$) or heavy water (deuterium, $2H_2O$) and antipyrine are used.

Measurement of Extracellular fluid volume:

- Radioactive sodium (^{22}Na), radioactive chloride, radioactive iothalamate, thiosulfate and inulin are used.

Measurement of Intracellular volume:

- Intracellular volume = total body water - extracellular volume.

Measurement of plasma volume:

- Serum albumin and evans blue dye (T - 1824) are used.

Volume	Indicators
Total body water	^3H_2O, ^2H_2O, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as total body water - Extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824
Blood volume	^{51}Cr-labeled red blood cells, or calculated as blood volume = Plasma volume/(1 − Hematocrit)
Interstitial fluid	(Calculated as extracellular fluid volume − Plasma volume)

Measurement of Body Fluid Volumes

Measurement of interstitial Fluid volume:

- Interstitial fluid volume = Extracellular fluid volume - plasma volume

Measurement of Blood volume:

- Radioactive chromium (^{51}Cr) can be used or can be calculated as,
  Blood volume = plasma volume / 1 - Hematocrit

Osmolality:

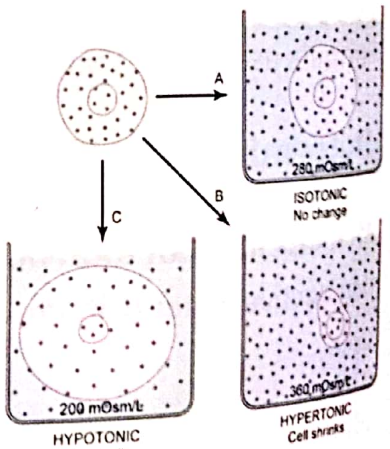
- When concentration is expressed as osmoles per kg of water.

Osmolarity:

- When concentration is expressed as osmoles per liter of solution.

Calculation of the Osmolarity and pressure of a solution:

- By using van't huff's Law, we calculate the potential osmotic pressure of a solution, assuming that the cell membrane is impermeable to solute.
- For sodium chloride osmotic coefficient is about 0.93.
- For each milliosmole concentration gradient of an impermeant solute about 19.3 mmHg of osmotic pressure is exerted across cell membrane.
- About 80% of total Osmolarity of interstitial fluid and plasma is due to sodium and chloride ions.
- For intracellular fluid half Osmolarity is due to potassium ion.



Effects of Different Solutions on cell volume

Types of solutions:

Isotonic solutions:

- Solutions having Osmolarity of 282 mOsm/L.
- e.g. 0.9% solution of NaCl and 5% Glucose solution.

Hypotonic solutions:

- Solutions having Osmolarity less than 282 mOsm/L.
- e.g. solution of NaCl with a concentration less than 0.9%

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- If a cell is placed in a hypotonic solution cell will swell up.

Hypertonic solutions:

- Solutions having Osmolarity greater than 282mosm/L.
- e.g. NaCl solution with a concentration greater than 0.9%.
- If a cell is placed in a hypertonic solution cell will shrink.

Changes in Fluid volume and body Osmolarity:

- A net gain of fluid by the body increases extracellular volume and net loss decreases extracellular volume.
- Intracellular volume is only altered if extracellular osmolality changes. If extracellular fluid osmolality increases, cells lose water and shrink. If extracellular fluid osmolality decreases, cells gain water and swell up.
- Gain of isotonic solution cause an increase in extracellular fluid volume with no change in body Osmolarity and intracellular fluid volume.
- Gain of hypotonic solution cause an increase in both extracellular and intracellular fluid volume and a decrease in body Osmolarity.
- Gain of hypertonic solution cause an increase in extracellular fluid volume and in body Osmolarity and a decrease in intracellular fluid volume.
- Loss of isotonic fluid such as in hemorrhage, diarrhea and vomiting cause a decrease in extracellular fluid volume with no change in body Osmolarity and intracellular volume.
- Loss of hypotonic fluid such as in dehydration, diabetes insipidus and alcoholism cause a decrease in extracellular and intracellular fluid volume with a rise in body Osmolarity.

Hyponatremia:

- When plasma sodium concentration becomes less than the normal (142 mEq/L).

Causes:

- Dehydration
- Diarrhea
- Vomiting
- Addison's disease
- Overuse of diuretics
- Over hydration

Symptoms:

- Nausea and vomiting
- Brain cell edema.
- seizures
- Coma
- Death

Correction:

- The rate of sodium correction should be 8-12 mEq/L in the first 24 hours and less than 1 mEq/L in 48 hours.

Hypernatremia:

- When plasma sodium concentration becomes elevated than normal.

Causes:

- Dehydration
- Diabetes insipidus
- Hypothalamic lesions
- Cushing's syndrome

Symptoms:

- Fever
- Intense thirst
- Hypernatremia is not more severe the reason is that sodium retention caused by increa aldosterone secretion also stimulates secretion of ADH and causes the kidneys to reab greater amount of water.

Correction:

- By infusion of hypotonic sodium chloride or dextrose solution.

Diabetes insipidus:

- Kidneys excrete large amount of dilute urine.
- Caused by lack of antidiuretic hormone.

Edema:

- It refers to the presence of excess fluid in the body tissues.

Causes of intracellular edema:

- Hyponatremia.
- Depression of metabolic system of tissues.
- Lack of adequate nutrition to cells.

Causes of extracellular edema:

- Abnormal leakage of fluid from plasma to the interstitial spaces across capillaries.
- Failure of lymphatic's to return fluid from interstitium back into blood called lymphede

Types of edema:

Pitting Edema:

- When a swollen part of the body has a dimple or indentation after pressing.

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Cause:

- Alteration in starling forces.

Non-Pitting Edema:

- When a swollen part of the body has no dimple or indentation after pressing.

Causes:

- Lymphatic obstruction
- Accumulation of osmotically active solutes in the interstitial space.

Generalized Edema:

- Also called anasarca.
- Swelling or edema is massive and generalized.

Causes:

- Heart failure
- Liver failure
- Kidney failure

Ascites:

- Accumulation of fluid occurs in the abdomen.

Cause:

- Chronic liver disease b/c plasma protein concentration falls.

Elephantiasis:

- It is a condition in which limb or other part of the body becomes grossly enlarged due to obstruction of the lymph vessels.

Causes:

- Filaria nematodes (wuchereria bancrofti) a microscopic worm.

Lymphangitis:

- It is an infection of lymph vessels.

Causes:

- Mostly from streptococcal and less often from staphylococcal infection.

Starling Equation:

- Mathematically capillary filtration rate can be expressed by an equation called starling equation.
- Filtration rate = $K_f \times (Pc - P_{if} - \pi_c + \pi_{if})$

In above equation,

- K_f is the capillary filtration coefficient which is defined as, the product of the permeab and surface area of the capillaries.
- Pc - Capillary hydrostatic pressure.
- P_{if} - Interstitial fluid hydrostatic pressure.
- π_c - Capillary plasma colloid osmotic pressure.
- π_{if} - interstitial fluid colloid osmotic pressure, which is zero .

Factors Affecting GFR:

- Increased Bowman's capsule hydrostatic pressure decreases GFR.
- Increased glomerular capillary colloid osmotic pressure decreases GFR.
- Increased glomerular capillary hydrostatic pressure increases GFR.

Safety factors that prevent Edema:

- Low tissue compliance in negative pressure range about 3mmHg.
- Lymphatic flow driven by the tissue pressure about 7 mmHg.
- Wash down of interstitial fluid protein by lymph about 7 mmHg.
- Total safety factor against edema is about 17mmHg.

Metabolic waste products:

- Urea comes from metabolism of amino acids.
- Creatinine form muscle creatin metabolism.
- Uric acid from nucleic acids metabolism.
- Bilirubin from hemoglobin metabolism.

Renin:

- Renin is an enzyme comes from juxtaglomerular apparatus.
- Renin converts angiotensinogen into angiotensin I, which is converted into angiotensin II by angiotensin converting enzyme (ACE) secreted in the lungs.
- Angiotensin II is the vasoactive product.

Regulation of Renin secretion:

- Regulators of renin secretion are,
- Perfusion pressure of the kidney is inversely related to renin secretion.
- Sympathetic stimulation of the kidney is directly related to renin secretion.
- Sodium delivery to macula densa is inversely related to renin secretion.

Macula densa:

- It is an area of closely packed specialized cells lining the wall of distal tubule, at the point where the thick ascending limb of loop of henle meets with the distal convoluted tubule.
- The cells of macule densa are sensitive to sodium concentration.
- A decrease in sodium concentration initiates a signal from macula dense that has two effects.

i) It decreases resistance to blood flow in afferent arterioles.
ii) It increases renin release from juxtaglomerular cells.

Juxtaglomerular Apparatus:

- It is a structure in the kidney that regulates the function of each nephron.

Types of cells in juxtaglomerular apparatus:

- It consist of three types of cells,
- Macula densa
- Juxtaglomerular cells which secrete renin.
- Extra glomerular mesangial cells.

Mesangial cells:

- These are specialized cells in the kidney that make up the mesangium of the glomerulus.
- Accounts for 30-40% of total cells in the glomerulus.

Mesangium:

- It is a space which is continuous with the smooth muscles of arterioles.
- It is outside the capillary lumen, but surrounded by capillaries.
- It is in the middle b/w capillaries.

Types of mesangial cells:

Extraglomerular mesangial cells:

- Also known as polkissen cells.
- These cells are found b/w afferent and efferent arterioles toward the vascular pole golmerulus.

Functions:

- Play a role in autoregulation of blood flow to the kidney and regulation of systemic pressure through the renin angiotensin system.

Intra glomerular mesangial cells:

- These cells are located inside the glomerulus and in b/w capillaries.

Functions:

- Structural support of glomerular capillaries.
- Regulation of glomerular filtration rate.
- Mesangial matrix formation.
- Phagocytosis.
- Monitoring of capillary lumen glucose concentration.
- Also has contractile activity.

Podocytes:

- These cells lining the bowman's capsule in the nephrons of the kidney.
- Together with the endothdial cells of the glomerular capillary loop and the glomer basement membrane, they from a filtration barrier.
- Cooperate with mesangial cells to support the structure and function of glomeru

Erythropoietin:

- It is a hormone comes from endothelial cells of peritubular capillaries network.
- It stimulates production of red blood cells by hematopoietic stem cells in the bo

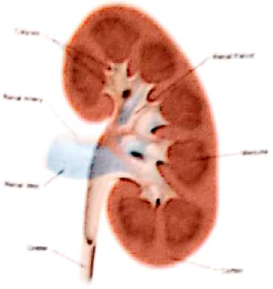
Regulation of 1, 25-dihydroxy vitamin D_3 production:

- Inactive vitamin D is converted into active vitamin D by proximal convoluted cel have α-1 hydroxylase enzyme.
- α-1 hydroxylase enzyme is stimulated by parathyroid hormone.
- Active from of vitamin D is 1, 25-dihydroxy vitamin D3 or calcitriol.

- It is essential for normal calcium deposition in bone and calcium reabsorption in GIT.

Kidneys:

- Kidneys lie on posterior wall of abdomen, outside the peritoneal cavity.
- Each kidney of the adult human have weight about 150g.


Structure of Human Kidney

Structure:

- Each kidney is composed of three main parts,

Renal cortex:

- It is the outer part of the kidney.
- It contains proximal convoluted tubule, distal convoluted tubule and proximal segment of the collecting tubule.

Renal medulla:

- It is the inner portion of the kidney.
- The medulla of the kidney is divided into 8 to 10 cone shaped masses of tissue called renal pyramids.
- It contains loop of henle and distal segment of the collecting tubule.

Renal pelvis:

- It is the expanded portion of ureter present at the center of the kidney.

Kidney innervation:

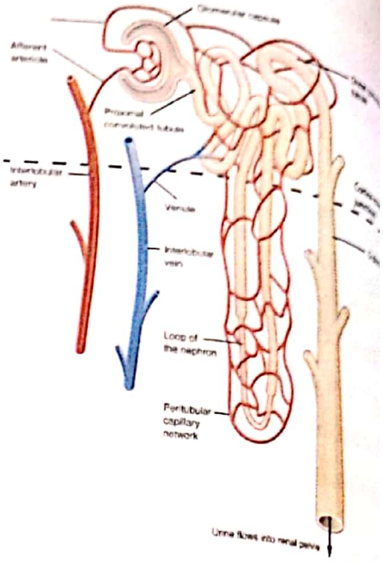
- Have sympathetic innervation.
- No parasympathetic innervation.

Kidney blood supply:

- Blood flow to both the kidneys is normally about 22% of cardiac output or 1100 ml/min.
- Pathway of blood flow is,
- Renal arty - Inter-lobar arteries - Arcuate arteries - Interlobular arteries (radial arteries) - Afferent arterioles - Glomerular capillaries - Efferent arterioles - peritubular capillaries - interlobular vein - Arcuate vain - Inter-lobar vain - renal vain.
- The renal circulation is unique in having two capillary beds, the glomerular and peritubular capillaries, which are arranged in series and separated by efferent arterioles.
- Hydrostatic pressure in glomerular capillaries is about 60 mmHg whereas hydrostatic pressure in peritubular capillaries is about 13 mmHg.
- Arcuate arteries and veins are formed at the boundary of renal cortex and renal medulla.
- The glomerular capillaries are covered by epithelial cells.

Nephron:

- ➢ The nephron is the Functional unit of the kidney.
- ➢ Each human kidney contains about 800,000 to 1000,000 nephrons.
- ➢ Kidneys cannot regenerate new nephrons.



Structure of Nephron

Structure of nephron:

- ➢ Each nephron is composed of renal corpuscle and renal tubules.

Renal corpuscle:

- ➢ It is composed of glomerulus and Bowman's capsule.

Glomerulus:

- ➢ It is a network of small blood vessels that are located b/w afferent and efferent arterioles.
- ➢ It filters the blood.

Bowman's capsule:

- ➢ It is a cup like sac surrounding the glomerulus.

Renal tubules:

- ➢ It is composed of,
- ➢ Proximal convoluted tubules
- ➢ Loop of Henle
- ➢ Distal convoluted tubules
- ➢ Collecting tubules
- ➢ Collecting ducts
- ➢ In each kidney there are about 250 large collecting ducts, each of which collects urine from about 400 nephrons.

Types of Nephron:

- ➢ There are two types of nephron,

Cortical nephron:

- ➢ Has short loop of henle that penetrates only the outer renal medulla.
- ➢ About 70% of nephrons are cortical.
- ➢ Supplied by an extensive network of peritubular capillaries.
- ➢ Major function is excretion of waste products in urine.

Juxtamedullary Nephron:

- ➢ Has long loop of henle, extending deep into the renal medulla.
- ➢ About 20-30% of nephrons are juxta medullary.

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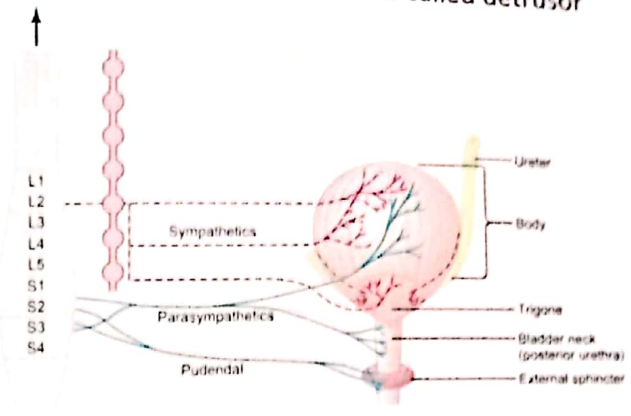
- Supplied by vasa recta, for which long efferent arterioles extend from glomeruli down into outer medulla and their divide into specialized peritubular capillaries called vasa recta.
- Major function is to concentrate urine by counter current mechanism.

Physiological anatomy of the bladder:

- Muscles of body and neck of the bladder are smooth muscles which are called detrusor muscle.
- When its fibers contract can increase pressure in the bladder up to 40 - 60 mmHg.
- Muscle of the external sphincter of bladder is voluntary skeletal muscle.
- Micturition is the process of emptying of bladder.
- On the posterior wall of the bladder, lying above the bladder neck is a small triangular area called trigone.
- The two ureters enter the bladder at the uppermost angles of the trigone.
- The trigone mucosa is smooth in contrast to the remaining bladder mucosa which is folded to from rugae.



Urinary Bladder and Its innervation

Nerve supply of urinary bladder:

- Somatic innervation through pudendal nerve connecting with cord segments S_2 and S_3 innervates the external urethral sphincter.
- Parasympathetic innervation through pelvic nerves innervates detrusor muscle and internal urethral sphincter.
- Sympathetic innervation through hypogastric nerve connecting with the L_2 segment of spinal cord innervates detrusor muscle and internal urethral sphincter.

Ureter:

- There is no significant change in the composition of urine as it flows through the renal calyces and ureter.
- In adults ureter is normally 25 - 35 cm (10 - 14 inches) long.
- The walls of the ureter contain smooth muscle and are innervated by both sympathetic and parasympathetic nerves, as well as by an intramural plexus of neurons.
- Peristaltic contractions in ureters are enhanced by parasympathetic stimulation and inhibited by sympathetic stimulation.

Vesicoureteral reflux:

- In some people, the distance that the ureter courses through the bladder wall is less than normal, thus contraction of the bladder during micturition does not always lead to complete occlusion of the ureter.

- As a result some of the urine in the bladder is propelled backward into the ureter, a condition called vesicoureteral reflux.

Ureterorenal reflex:

- The ureters are well supplied with pain nerve fibers.
- When a ureter becomes blocked e.g: by a ureteral stone, intense reflex constriction occurs which is associated with severe pain.
- These pain impulses cause a sympathetic reflex back to the kidney to constrict the renal arterioles, thereby decreasing urine output from the kidney. This effect is called the uretero renal reflex.

Micturition waves:

- Beyond 300 – 400 ml of urine, collection of more urine in the bladder causes the pressure to rise rapidly, these pressure peaks are called micturition waves and are caused by the micturition reflex.

Cystometrogram:

- It is a test used to look for problems with the filling and emptying of the bladder.
- During this test a catheter with attached manometer is placed in the bladder and the bladder is filled slowly with fluid while its internal pressure is recorded.
- This gives information about bladder capacity, leak point and pressure at various stages of filling.

Micturition reflex:

- Micturition contractions are the result of a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures.
- Sensory signals from bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexly back again to bladder through the parasympathetic nerve fibers by way of these same nerves.

Tabetic bladder:

- Syphilis can cause constrictive fibrosis around dorsal root nerve fibers destroying it, this condition is called tabes dorsalis.
- Bladder becomes distended and thin walled.
- Characterized by difficulty in urination and increased residual urine which could lead to urinary retention with over flow incontinence.

Atonic bladder:

- A bladder whose muscles do not fully contract.

- Difficulty in urination.
- It occurs during the phase of spinal shock immediately after the injury.
- The bladder wall muscle is relaxed, the sphincter vesicae tightly contracted and the sphincter urethra relaxed.
- The bladder becomes greatly distended and finally over flows.

Automatic reflex bladder:

- It occurs when patient has recovered from spinal shock, provided that cord lesion lies above the level of the parasympathetic out flow (S_2, S_3 and S_4).
- It is the type of bladder normally found in infancy.
- The bladder fills and empties reflexly.

Autonomous bladder:

- It occurs if the sacral segments of the spinal cord are destroyed.
- The bladder is without any external reflex control.
- The bladder wall is flaccid and the capacity of the bladder is greatly increased.
- It merely fills to capacity and continual dribbling is the result.
- The bladder may be partially emptied by manual compression of the lower part of the abdominal wall.

Glomerular filtration rate:

- It is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time.
- The GFR is about 125 ml/min or 180 L/day.
- Reabsorption is 124 ml/min or 178.5 L/day.
- Excretion is 1 ml/min or 1.5 L/day.
- GFR is about 20% of renal plasma flow.
- GFR = k_f x Net filtration pressure.

Filtration fraction:

- It is the fraction of renal plasma flow that is filtered.
- It is about 0.2 or 20% of renal plasma flow.
- Can be increased either by raising the GFR or by reducing renal plasma flow.
- It can be calculated as, Filtration fraction = GFR / Renal plasma flow

Glomerular capillary membrane:

- It has three instead of usual two major layers,
- The endothelium of the capillary
- Basement membrane.
- Layer of epithelial cells (podocytes) surrounding the outer surface of basement membrane.

Barriers to plasma protein filtration:

- Barriers that prevent plasma protein filtration are,
- Endothelial cell proteins have negative charges that prevent the passage of plasma proteins.
- The basement membrane prevents filtration of plasma proteins, b/c of strong negative electrical charges associated with the proteoglycans of basement membrane.
- The epithelial cells which have negative charges prevent filtration of plasma proteins.

Urinary excretion rate:

- Urinary excretion rate = filtration rate – reabsorption rate + secretion rate

Renal plasma flow:

- Renal plasma flow = Renal blood flow x (1- Hematocrit)

Filterability of solutes:

- A filterability value of 1 means that the substance is filtered as freely as water.
- A value of 0 indicates that it is not filtered.
- A value of 0.75 means that the substance is filtered only 75% as rapidly as water.
- Positively and neutral charged large molecules are filtered more easily than negatively charged molecules of equal molecular weight.
- Albumin is prevented from filtration by its negative charge and electrostatic repulsion exerted by negative charges of the glomerular wall.

Substance	Filterability
Water	1.0
Sodium	1.0
Glucose	1.0
Inulin	1.0
Myoglobin	0.75
Albumin	0.005

Filtration coefficient:

- It is defined as, the product of permeability and surface area of the capillaries.
- As, GFR = K_f × Net filtration pressure
- Filtration coefficient (K_f) can be expressed as,

$$K_f = GFR / \text{Filtration pressure}$$

- Normal k_f for kidney is 12.5 ml/min/mmHg.
- When k_f is expressed per 100g of kidney weight it is about 4.2 ml/min/mmHg.
- The average k_f of other tissues in the body is about 0.01 ml/min/mmHg per 100 grams.
- Increased k_f raises GFR and decreased k_f reduces GFR.
- Chronic uncontrolled hypertension and diabetes mellitus gradually reduce k_f by increasing the thickness of glomerular capillary basement membrane.

Effect of constriction of afferent arterioles on GFR:

- Constriction of afferent arterioles reduces GFR.

Effect of constriction of efferent arterioles on GFR:

- At moderate level of efferent arteriolar constriction there is a slight increase in GFR, but with severe constriction there is decrease in GFR, b/c rise in colloid osmotic pressure exceeds the increase in glomerular capillary hydrostatic pressure caused by efferent arteriolar constriction.

Effect of sympathetic system on GFR:

- Stimulation of the renal sympathetic system can constrict the renal arterioles and decrease renal blood flow and GFR.

Vasoconstrictors of Afferent arterioles:

- These substances decrease GFR.
- Vasoconstrictors of afferent arterioles are,
- Epinephrine
- Nor epinephrine
- Endothelin

Vasoconstrictors of efferent arterioles:

- Vasoconstrictor of efferent arterioles is angiotensin II which prevent decrease in GFR.

Effect of autacoids on GFR:

- Nitric oxide, prostaglandins (PGE_2 and PGI_2) and bradykinin decrease renal vascu resistance and increase GFR.
- Under stressful conditions such as volume depletion or after surgery, the administration non-steroidal anti-inflammatory drugs such as aspirin inhibits prostaglandin synthesis m cause significant reductions in GFR.

Tubuloglomerular feedback of GFR:

- The juxtaglomerular complex consists of macula densa cells in the initial portion of th distal tubule and juxtaglomerular cells in the wall of the afferent and efferent arterioles.
- Angiotensin converting enzyme inhibitors may cause greater reduction in GFR, so thes drugs are used to treat patients who have hypertension.
- High protein intake and increased blood glucose, increase renal blood flow and GFR b amino acids, glucose and sodium are reabsorbed together by the proximal tubules Increased A.A and glucose reabsorption also stimulates sodium reabsorption in th proximal tubules.
- This reabsorption of sodium decreases sodium delivery to the macula densa which elicits tubuloglomerular feedback mediated decrease in resistance of the afferent arterial.
- The decreased afferent arteriolar resistance then raises renal blood flow and GFR.

Autoregulation of Renal blood flow and GFR:

- The ability of the kidney to maintain constancy of the GFR over a wide range of rena perfusion pressure is called autoregulation.
- Mechanism is the ability of blood vessels to resist stretching during increased arteria pressure called renal myogenic response.

Minimal change nephropathy:

- Negative charges on the basement membrane are lost.
- Large amount of protein is lost in the urine, a condition called proteinuria.
- Most common cause of nephrotic syndrome.

Causes:

- An immunological response with abnormal T- cell secretion of cytokines that neutralize th negative charge of glomerular filtering system.

Nephrotic syndrome:

- Injury to the glomerular epithelium or basement membrane occurs.
- Loss of protein occurs in urine but no red blood cells.

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Nephritic syndrome:

- It is an inflammatory response to the glomerular injury.
- Protein and red blood cells leak form the blood stream into the urine.
- Decreases efficiency of the kidney.

Factors that can decrease the GFR:

- Renal disease
- Diabetes mellitus
- Hypertension
- Urinary tract obstruction.
- Decreased renal blood flow.
- Increased plasma protein.
- Decreased arterial pressure.
- Decreased angiotensin II.
- Increased sympathetic activity.

Hormones and autacoids that influence GFR:

Hormones or autacoids	Effect on GFR
Norepinephrine	Decreases GFR
Epinephrine	Decreases GFR
Endothelin	Decreases GFR
Angiotensin II	prevent decrease in GFR
Nitric oxide	Increase GFR
Prostaglandins	Increases GFR

Filtration load:

- It is the amount of a substance filtered per unit time.
- Can be calculated as,

Filtration load = GFR × Plasma concentration of the substance

- The filtered load of glucose is about 125 mg/min.
- As, Filtered load = GFR × Plasma glucose

= 125 ml/min × 1 mg/ml

= 125 mg/min

Primary active transport:

- It is the transport coupled directly to an energy source, such as hydrolysis of ATP.
- e.g: Na^+- K^+ ATPase pump, H^+ - K^+ ATPase and calcium ATPase pump.

Secondary active transport:

- It is the transport coupled indirectly to an energy source, such as due to an ion gradient.
- e.g: Co-transport of sodium and glucose in proximal tubule.

Transport maximum:

- It is the highest rate in mg/min at which the renal tubules can transfer a substance fro the tubular fluid into interstitial fluid or from interstitial fluid into the tubular luminal flu beyond which it may be excreted in urine.
- It mostly occurs for substances that are actively reabsorbed or secreted.
- The limitation is due to saturation of the specific transport systems involved when t amount of solute delivered to the tubule exceeds the capacity of the carrier proteins a specific enzymes involved in the transport process.
- In human the transport maximum for glucose averages about 375 mg/min.

Threshold for Glucose:

- It is defined as, the plasma concentration of glucose at which glucose first appears in th urine.
- It is about 250 mg/100mL or 250 mg/dL.

Transport maximum for substances:

Substance	Transport maximum
Glucose	375 mg/min
Phosphate	0.01 mmol/min
Amino acids	1.5 mmol/min
Plasma proteins	30 mg/min
Creatinine	16 mg/min
Para-aminohippuric acid	80 mg/min

Gradient time transport:

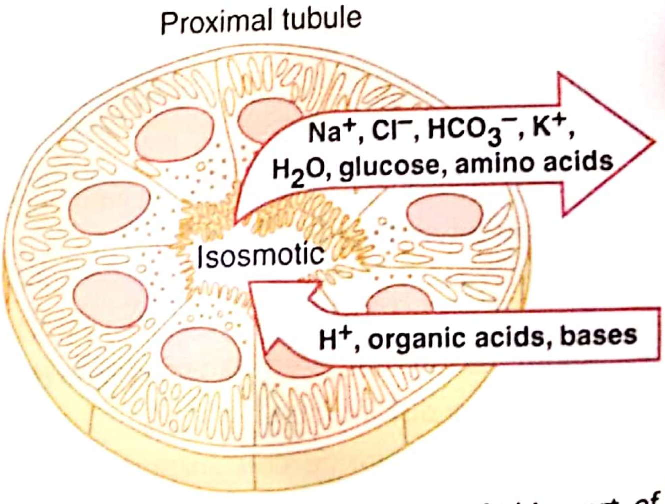
- Substances that are passively reabsorbed do not demonstrate a transport maximum b/c their rate of transport is determined by other factors such as,
- Electrochemical gradient for diffusion of the substance across the membrane.
- Permeability of membrane for the substance.
- Time that the fluid containing the substance remains within the tubule.
- e.g: Sodium transport in the proximal tubules obeys gradient time transport.

Solvent drag:

- The movement of ions across cell membrane by bulk transport following the flow of water rather than being facilitated by ion channels or cellular pumps.

Reabsorption and secretion along renal tubules:

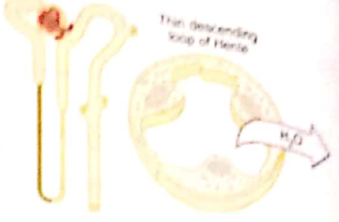
- In proximal tubule, the water permeability is high and water is reabsorbed as the solutes.
- In ascending loop of henle, water permeability is low and no water is reabsorbed despite a large osmotic gradient.
- In distal tubule, collecting tubules and collecting ducts water permeability can be high or low depending on the presence or absence of ADH.


Proximal tubule
Na^+, Cl^-, HCO_3^-, K^+, H_2O, glucose, amino acids
Isosmotic
H^+, organic acids, bases

Role of proximal convoluted tubule:

- About 65% of the filtered load of sodium and water and a less amount of filtered chloride are reabsorbed by proximal tubule.
- Total solute concentration remains same all along the proximal tubule b/c of extremely high permeability of this part of nephron to water.

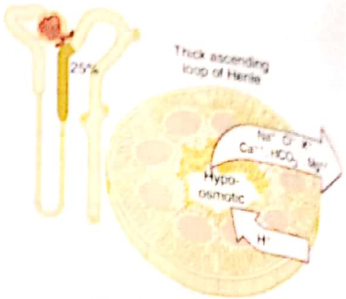
- para-aminohippuric acid is rapidly secreted by proximal tubule from blood into tubular fluid, and the rate of PAH clearance can be used to estimate renal plasma flow.



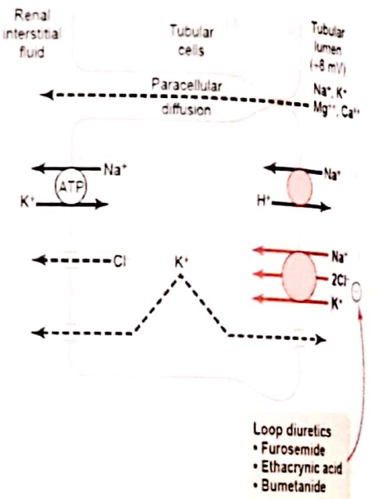
Role of loop of Henle:

Transport ch

- About 20% of filtered water is reabsorbed in the thin descending limb of loop of henle.
- The ascending limb including both the thin and thick portions, are impermeable to water.
- About 25% of filtered load of sodium, chloride and potassium are reabsorbed in the loop of henle, mostly in the thick ascending limb. Some amount of other ions such as calcium, bicarbonate and magnesium are also reabsorbed in the thick ascending loop of henle.

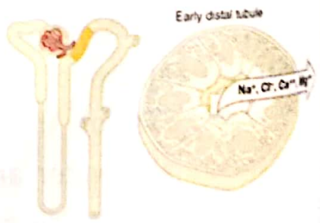


- The thin segment of the ascending limb has much lower reabsorptive capacity than does the thick segment, and does not reabsorb significant amount of any solute.
- An important component of solute reabsorption in the thick ascending limb is Na^+ - K^+ ATPase pump in the epithelial cell basolalateral membranes.
- In the thick ascending loop, movement of sodium across the luminal membrane is mediated by 1- Sodium, 2- Chloride, 1- Potassium co-transporter.
- The thick ascending limb of loop of henle is the site of action of the powerful loop diuretics furosemide, ethacrynic acid and bumetanide, all of which inhibit the action of 1- sodium, 2-chloride, 1- potassium co-transporter.



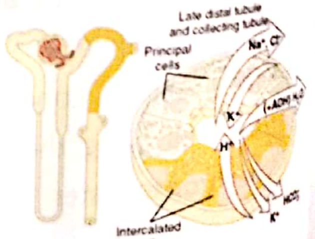
Mechanisms of sodium, chloride and potassium transport in the thick ascending loop of Henle.

- The thick ascending limb has a sodium-hydrogen counter transport mechanisum in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment.
- The tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule.



Role of Distal Tubules:

- About 5% of the filtered load of sodium chloride is reabsorbed in the early distal tubule.
- The sodium chloride co-transporter moves sodium chloride form tubular lumen into the cell. The sodium-potassium ATPase pump transports sodium out of the cell across the basolateral membrane.



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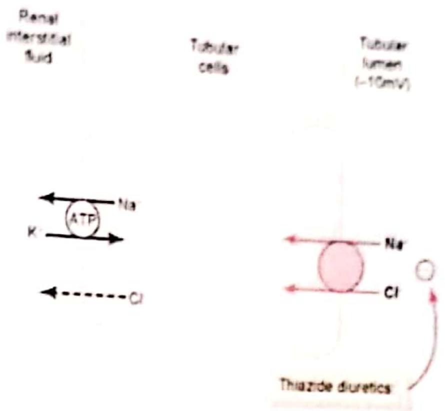
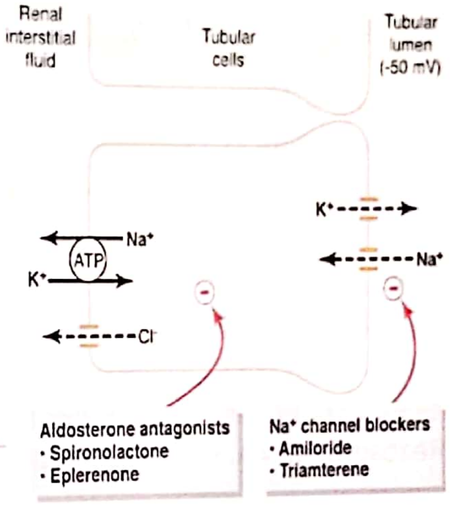
- Chloride diffuses out of the cell into the renal interstitial fluid through chloride channels in the basolateral membrane.
- The thiazide diureties, which are used to treat hypertension and heart failure, inhibit the sodium-chloride co-transporter.
- Late distal tubule and cortical collecting tubule are composed of two types of cells, the principal cells and intercalated cells.



Mechanism of sodium chloride transport in the early distal tubule

Role of Principal cells:

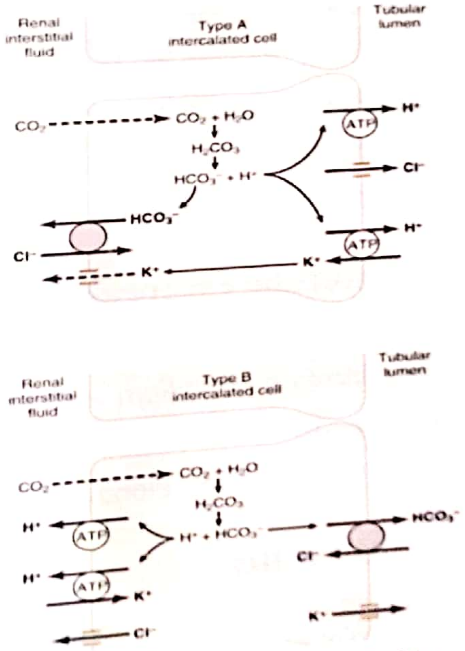
- Principal cells reabsorb sodium and water from the lumen and secrete potassium ions into the lumen, which depend on Na^+- K^+ ATPase pump in each cell basolateral membrane.
- Principal cells are the primary sites of action of potassium sparing diuretics, including spironolactone, eplerenone, amiloride and triamterene.
- Spironolactone and eplerenone are aldosterone antagonists.
- Amiloride and triamterene are direct sodium channel blockers.



Mechanism of sodium chloride reabsorption and potassium secretion in the principal cells

Role of Intercalated cells:

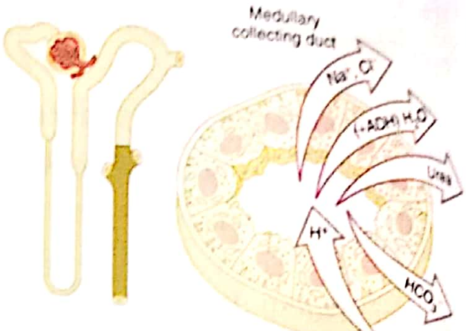
- Responsible for acid base regulation.
- There are type A and type B intercalated cells.
- Type A intercalated cells eliminate hydrogen ions while reabsorb bicarbonate ions in acidosis. These cells secrete hydrogen ions by a hydrogen ATPase transporter and a hydrogen potassium ATPase transporter.
- Type B intercalated cells secrete bicarbonate ion into the tubular lumen while reabsorb hydrogen ions in alkalosis. These cells have hydrogen and bicarbonate transporters on opposite sides of the cells membrane compared with type A cells.



Type A and Type B intercalated cells of the collecting tubule.

Role Medullary collecting duct:

- It is permeable to urea and some reabsorption of urea occurs here and contributes in hyperosmotic renal medullary interstitium.
- Reabsorb about 5% of the filtered water and sodium.
- Final site of the kidney tubule to influence body electrolyte and fluid balance.



Transport characteristics of the medullary collecting duct.

Golmerulotubular balance:

- It is the intrinsic ability of the tubules to increase their reabsorption rate in response to increased tubular inflow.
- e.g: If GFR increases from 125 ml/min to 150 ml/min, the absolute rate of proximal tubular reabsorption also increases from about 81 ml/min (65% of GFR) to about 97.5 ml/min (65% of GFR). It shows that the total rate of reabsorption increases as the filtered load increases.

Reabsorption rate:

- The normal rate of peritubular capillary reabsorption is about 124 ml/min.
- Reabsorption can be calculated as,

Reabsorption = k_f x Net reabsorptive force.

- Net reabsorptive force represents the sum of hydrostatic and colloid osmotic forces that favor or oppose reabsorption across the peritubular capillaries.
- These forces include,
- Hydrostatic pressure inside the peritubular capillaries which oppose reabsorption.
- Hydrostatic pressure in the renal interstitium which favors reabsorption.
- Colloid osmotic pressure in the peritubular capillaries which favors reabsorption.
- Colloid osmotic pressure in the renal interstitium which opposes reabsorption.

Aldosterone Escape:

- Small increase in glomerular filtration that follow increases in renal arterial pressure cause large increase in sodium and water excretion in urine, called pressure natriuresis and pressure diuresis respectively, and blood pressure becomes normal.
- This return to normal blood pressure is called aldosterone escape.

Aldosterone:

- Secreted by the zone glomerulosa cells of adrenal cortex.
- An important regulator of sodium reabsortption and secretion of potassium and hydrogen ions in the renal tubules.

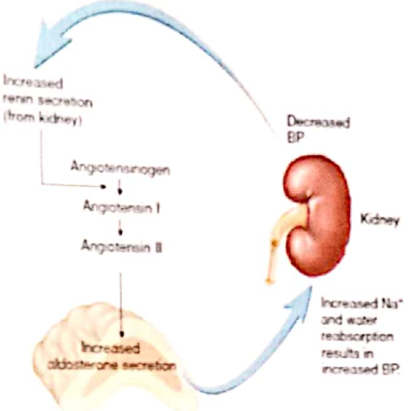
- Mechanism by which aldosterone increases sodium reabsorption and potassium secretion is by stimulating the sodium-potassium ATPase pump on basolaterial side of cortical collecting tubules.
- It also increases the sodium permeability of the luminal side of the membrane.
- A major renal tubular site of aldosterone action is on the principal cells of cortical collecting tubule.

Stimuli for aldosterone secretion:

- The most important stimuli for aldosterone secretion are,
- Increased extracellular potassium concentration
- Increased angiotensin II level.

Antidiuretic Hormone:

- Secreted by posterior lobe of pituitary gland.
- Increases water reabsorption.


Increased renin secretion (from kidney)
Decreased BP
Angiotensinogen
Angiotensin I
Angiotensin II
Kidney
Increased Na⁺ and water reabsorption results in increased BP.
Increased aldosterone secretion

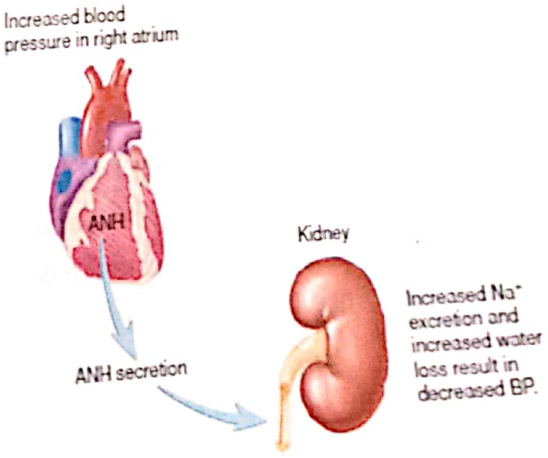
Effects of aldosterone on blood Pressure

Mechanism of action of ADH:

- ADH binds to specifics V_2 receptors in late distal tubule, collecting tubules and collecting ducts, increases formation of CAMP and activating protein kinases.
- This stimulates the movement of an intracellular protein called aquaporin-2 to the luminal side of cell membranes.
- The molecules of AQP-2 cluster together and fuse with cell membrane by exocytosis to from water channels that permit rapid diffusion of water through the cells.
- When concentration of ADH decreases the molecules of AQP-2 are shuttled back to the cell cytoplasm removing the water channels from luminal membrane and reducing water permeability.

Atrial Natriuretic peptide:

- When specific cells of the cardiac atria are stretched b/c of plasma volume expansion and increased atrial blood pressure, they secrete a peptide called ANP.
- ANP inhibits the reabsorption of sodium and water by the renal tubules.
- ANP also inhibits renin secretion and therefore angiotensin II formation, which in turn reduces renal tubular reabsorption.
- This decreased sodium and water reabsorption increases urinary excretion, which helps to return blood volume back toward normal.


Increased blood pressure in right atrium
ANH
Kidney
Increased Na⁺ excretion and increased water loss result in decreased BP.
ANH secretion

Effects of ANP on Blood pressure

Effects of parathyroid hormone:

- Increases tubular reabsorption of calcium.
- Inhibit reabsorption of phosphate.
- Stimulate magnesium reabsorption in the loop of henle.

Sympathetic activity increases sodium reabsorption:

- Activation of sympathetic nervous system decrease sodium and water excretion b constricting the renal arterioles, thereby reducing the GFR.
- Also increases renin release and angiotensin II formation which increase reabsorption an decrease renal excretion of sodium.

Diabetes insipidus:

- Kidneys excrete large amount of dilute urine.
- Permeability of the distal tubules and collecting ducts to water is low.
- Due to absence of ADH.

Clearance rate:

- It is the volume of plasma that is completely cleared of the substance by the kidneys pe unit time.
- There is no single volume of plasma that is completely cleared of the substance, rena clearance provides a useful way of quantifying the excretory function of the kidneys.
- Mathematically, $C_S \times P_S = U_S \times V$

  So, $C_S = U_S \times V / P_S$
- Thus renal clearance of a substance is calculated from the urinary excretion rate ($U_S \times V$) that substance divided by its plasma concentration.

In the above equation,

- Cs = clearance rate of a substance
- Ps = plasma concentration of the substance
- Us = urine concentration of the substance
- V = urine flow rate

Inulin clearance can be used to estimate GFR:

- If a substance is freely filtered and is not reabsorbed or secreted by the renal tubules, th the rate at which that substance is excreted in urine ($Us \times V$) is equal to the filtration rate the substance by the kidneys ($GFR \times Ps$).
- Thus, $GFR \times Ps = Us \times V$
- The GFR can be calculated as the clearance of the substance as,

  $GFR = Us \times V/Ps = Cs$
- Inulin is a polysaccharide having molecular weight of about 5200, not produced in the bod
- Inulin must be administered intravenously to a patient to measure GFR.
- Radioactive iothalamate and creatinine are also used clinically to measure GFR.

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- Creatinine is a byproduct of muscle metabolism and is produced endogenously, b/c measurement of creatinine clearance does not require intravenous infusion into the patient, there for this method is much more widely used for estimating GFR clinically.

Clearance ratio:

- Clearance ration = Cs / C_{inulin}

Renal blood flow:

- Renal blood flow = RPF / 1 - Hematocrit

Excretion rate:

- Excretion rate = Us × V

PAH clearance can be used to estimate RPF:

- Para-aminohippuric acid is about 90% cleared from the plasma, therefore the clearance of PAH can be used to estimate renal plasma flow.
- If a substance is completely cleared from the plasma, the clearance rate of that substance is equal to the total RPF.
- In other words, the amount of the substance delivered to the kidneys in blood (RPF ×Ps) would be equal to the amount excreted in the urine (Us × V).
- Thus RPF can calculated as, RPF = Us × V/Ps = Cs
- Total renal plasma flow is 650 ml/min.

Filtration fraction:

- Filtration rate can be calculated as ,

FF = GFR / RPF

= 125/650

= 0.19 or 0.2 or 20%

Reabsorption rate:

- Reabsorption rate = Filtered load - Excretion rate
  = (GFR × Ps) - (Us × V).

Secretion rate:

- Secretion rate = Exertion rate - Filtered load.

Comparison of inulin clearance with clearances of other solutes:

- These results can be extract by comparing the clearance of a substance with clearance of inulin,

- If the clearance rate of the substance equals that of inulin, the substance is only
and not reabsorbed or secreted.
- If the clearance rate of a substance is less than inulin clearance, the substance must
been reabsorbed by the nephron tubules.
- If the clearance rate of a substance is greater than that of inulin, the substance mu
secreted by the nephron tubules.

Substance	Clearance rate ml/min
Glucose	0
Sodium	0.9
Chloride	1.3
Potassium	12
Phosphate	25
Inulin	125
Creatinine	140

Urine concentration and dilution:

- Tubular fluid remains isosmotic in proximal tubule, with Osmolarity of about 300 mOsm/L.
- Osmolarity of the tubular fluid flowing through the descending loop of henle increases b/c it is highly permeable to water.
- Tubular fluid is diluted in the ascending loop of henle, this portion of tubular segment is impermeable to water, even in the presence of large amounts of ADH, decreasing its Osmolarity to about 100 mOsm/L.
- Tubular fluid in distal and collecting tubules is further diluted in the absence of ADH, decreasing its Osmolarity to as low as 50 mOsm/L.
- The maximal urine concentrating ability of human kidney is 1200 mOsm/L.
- Normal human produces 600 mOsm/L of solute as waste product per day.

Obligatory urine volume:

- It is the minimal volume of urine that must be excreted per day, to eliminate waste product from the body.
- It is obtained by dividing the daily osmolar excretion by the maximum urine Osmolarity. therefore, 600 /1200 = 0.5 L/day
- So obligatory urine volume is 0.5L or 500ml.

Urine Specific gravity:

- It is a measure of the weight of solutes in a given volume of urine.
- It is determined by the number and size of the solute molecules.
- It is used in clinical to provide a rapid estimate of urine solute concentration.
- In most cases urine specific gravity increases linearly with increasing urine Osmolarity.
- Urine specific gravity is expressed in gram/mL.
- Inhuman it ranges from 1.002 to 1.028 g/mL.
- Dipsticks measure approximate urine specific gravity, but most laboratories measure specific gravity with a refractometer.

Requirements for excreting concentrated urine:

- The basic requirements for excreting concentrated urine are,
- High level of ADH, which increases the permeability of the distal tubules and collecting ducts to water.
- High Osmolarity of the renal medullary interstitial fluid, which provides the osmotic gradient necessary for water reabsorption.

Osmolarity of the renal medullary interstitium:

- It is normally hyperosmotic having Osmolarity of about 1200 - 1400 mOsm/L.
- This hyperosmolarity is generated by counter current multiplier system and urea recycling.
- This hyperosmolarity is maintained by counter current exchange in vasa recta.

Counter current multiplier system:

- The repetitive reabsorption of sodium chloride by the thick ascending loop of henle and continued in flow of new sodium chloride from the proximal tubule into the loop of henle is called counter current multiplier mechanism.
- The sodium chloride reabsorbed from the ascending loop of henle keeps adding to the newly arrived sodium chloride thus multiplying its concentration in the medullary interstitium.

Counter current Exchange in vasa recta:

- Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla.
- The vasa recta are highly permeable to solutes in the blood, except for plasma proteins.
- As blood descends into the medulla toward papillae, it becomes progressively more concentrated, partly by solute entry from intersititum and partly by loss of water into the interstituim.
- By the time the blood reaches the tips of vasa recta, it has a concentration of about 1200 mOsm/L, same as that of the medullary interstitium.
- As blood ascends back toward the cortex, it becomes progressively less concentrated as solute diffuse back out into the medullary interstitium and water moves into the vasa recta.
- Although large amounts of fluid and solute are exchanged across the vasa recta, there is little net dilution of the concentration of the interstitial fluid at each level of the renal medulla b/c of U- shape of vasa recta capillaries, which act as counter current exchangers.
- Thus the vasa recta do not create the medullary hyper-Osmolarity, but prevent it from being dissipated.

Recycling of urea contributes to hyperosmotic renal medullary interstitium:

- When there is water deficit and blood concentration of ADH is high, large amounts of urea are passively reabsorbed from the inner medullary ducts into interstitium by specific urea transporters, UT - A_1 and UT - A_3.
- Urea contributes 40-50% of Osmolarity of renal medullary interstitium.
- The concentration of urea continues to rise as the tubular fluid flows into the thin segments of the loop of henle partly b/c of water reabsorption out of descending loop of henle but also b/c some secretion of urea into the thin loop of henle from medullary interstitium by urea transporter UT - A_2.
- This urea then passes upward through the ascending loop of henle, the cortical collecting tubule and back down into the medullary collecting duct again.
- In this way, urea can recirculate through these terminal parts of tubular system several times before it is excreted.
- This urea recirculation provides an additional mechanism for forming a hyperosmotic renal medulla.

Osmolar clearance:

- It is the volume of plasma cleared of solutes each minute.
- The total clearance of solutes from the blood can be expressed as the osmolar clearance.
- It can be calculated in the same way as the clearance of a single substance is calculated,

$C_{osm} = U_{osm} \times V / P_{osm}$

- In the above equation,
- U_{osm} = urine osmolarity
- V = urine flow rate
- P_{osm} = plasma osmolarity

Free-water clearance (CH_20):

- It is the difference b/w water excretion (urine flow rate) and osmolar clearance.

So, $C_{H2O} = V - C_{osm}$

$= V - (U_{osm} \times V)/P_{osm}$

- Thus the rate of free water clearance represents the rate at which solute free water is excreted by the kidneys.
- When free water clearance is positive, excess water is excreted by the kidneys.
- When free water clearance is negative, excess solutes are removed from the blood by the kidneys and water is conserved.
- When urine Osmolarity is greater than plasma Osmolarity, free water clearance is negative, indicating water conservation.
- When urine Osmolarity is less than plasma Osmolarity, free water clearance is positive, indicating that water is removed from the plasma by the kidneys.

Central diabetes insipidus:

- An inability of ADH to release from posterior pituitary.
- Can be caused by head injuries, infection or it can be congenital.
- B/c the distal tubular segments cannot reabsorb water in the absence of ADH, results in the formation of large volume of dilute urine.

Treatment:

- Administration of a synthetic analogue of ADH, desmopressin which acts selectively on V_2 receptors to increase water permeability in late distal and collecting tubules.

Nephrogenic diabetes insipidus:

- An inability of the kidneys to respond to ADH.
- Nephrogenic diabetes insipidus can be distinguished from central diabetes insipidus by administration of desmopressin, the synthetic analogue of ADH.

Urine Concentration and Dilution

CH# 05

Estimating plasma Osmolarity from sodium concentration:

- In most clinical laboratories, plasma Osmolarity is not routinely measured, because and its associated anions account for about 94% of the solute in extracellular compar
- Plasma Osmolarity can be roughly estimated from plasma sodium concentration as,
- $P_{osm} = 2.1 \times P_{Na^+}$ (mmol/L).

ADH synthesis and secretion:

- ADH is synthesized in supraoptic nucleus of the hypothalamus.
- Decreased blood pressure, nausea, morphine and nicotine increase ADH secretion.
- Increased blood pressure, alcohol, clonidine and haloperidol decrease ADH secretion.

Regulation of potassium concentration:

- Insulin, aldosterone, β-adrenergic stimulation and alkalosis cause hypokalemia.
- Diabetes mellitus, Addison's disease, β-adrenergic blockade, acidosis, cell lysis, strenuous exercise and increased extracellular fluid Osmolarity cause hyperkalemia.
- The normal rate of potassium filtration by the glomerular capillaries is about 756 mEq/day, (GFR, 180 L/day multiplied by plasma potassium concentration 4.2 mEq/L).
- Type A intercalated cells reabsorb potassium while type B intercalated cells and principal cells secrete potassium.

Factor that can alter potassium distribution

Factors that shift K^+ into cells	Factors that shift k^+ out of cells
Insulin	Diabetes mellitus
Aldosterone	Aldosterone deficiency
β-adrenergic stimulation	β-adrenergic blockade
Alkalosis	cells lysis
Sternous exercise	

Calcium concentration:

- Normal extracellular fluid calcium ion concentration is 2.4 mEq/L.
- Hypocalcaemia cause excitability of nerve and muscle cells.
- Hypercalcemia depresses neuromuscular excitability.
- About 50% of calcium in the plasma exists in the ionized form, which has biological activity at cells membranes.
- The remainder is either bound to the plasma proteins (40%) or complexed in the non-ionized form with anions such as phosphate and citrate (10%).
- Changes in plasma hydrogen ion concentration can influence the degree of calcium binding to plasma proteins with acidosis less calcium is bound to the plasma proteins.
- With alkalosis greater amount of calcium is bound to plasma protein, there for patients with alkalosis are more susceptible to hypocalcemic teary.
- The usual rate of dietary calcium intake is about 1000 mg/day, with about 900 mg/day of calcium excreted in feces.

Regulation of calcium concentration:

- Parathyroid hormone maintains blood calcium level.
- About 60% of the plasma calcium can be filtered at the glomerulus. About 65% of the filtered calcium is absorbed in proximal tubule, 25 to 30% is reabsorbed in the loop of henle and 4 to 9% is reabsorbed in the distal and collecting tubules.
- Most of the calcium reabsorption in the proximal tubule occurs through the paracellular path way, it is dissolved in water and carried with reabsorbed fluid as it flow b/w cells. Only about 20% of proximal tubular calcium reabsorption occurs through the transcellular pathway.

- About 50% of calcium reabsorption in the thick ascending limb of loop of henle occurs through Paracellular route by passive diffusion and remaining 50% through the transcellular path way, a process that is stimulated by PTH.
- In the distal tubule calcium reabsorption occurs by active transport.

Factors that alter renal calcium Excretion:

Decrease calcium Excretion	increase calcium Excretion
Increase parathyroid hormone	Decrease parathyroid hormone
Decrease extracellular fluid volume	increase extracellular fluid volume
Decrease blood pressure	increase bold pressure
Increase plasma phosphate	decrease plasma phosphate
Metabolic alkalosis	metabolic acidosis
Vitamin D3	

Regulation of renal phosphate Excretion:

- Proximal tubule reabsorbs 75 to 80% of the filtered phosphate.
- Distal tubule reabsorbs about 10%.
- About 10% of the filtered phosphate is excreted in the urine.
- In proximal tubule phosphate reabsorption occurs through the transcellular pathway.
- PTH decreases tubular phosphate reabsorption and more phosphate is excreted.
- PTH decreases the transport maximum for phosphate by the renal tubules, so a great proportion of the tubular phosphate is lost in the urine.

Regulation of Renal magnesium Excretion:

- Plasma magnesium concentration is about 1.8 mEq/L.
- Normal daily intake of magnesium is about 300 mg/day.
- Proximal tubule reabsorbs about 25% of filtered magnesium.
- The primary site of magnesium reabsorption is the loop of henle where about 65% filtered magnesium is reabsorbed.

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ACID BASE REGULATION:

- It concerns the proper balance b/w acids and bases in the extracellular fluids.
- Metabolic processes continually produce acid and to a lesser extent base. Hydrogen ion especially reactive can attach to negatively charged proteins and alter their configuration and function. So its regulation is necessary.

Buffer systems in the body:

- There are three buffer systems in the body,
- Bicarbonate buffer system
- Phosphate buffer system
- Protein buffer system

Normal pH of body fluids:

Body fluid	pH
Arterial blood	7.40
Venous blood	7.35
Interstitial fluid	7.35
Intracellular fluid	6.0-7.4
Urine	4.5-8.0
Gastric HCL	0.8

i. Bicarbonate buffer system:

- It is the most important extracellular buffer system.
- The PK of the bicarbonate buffer system is 6.1.
- At a plasma PH of 7.4 the ratio of bicarbonate to carbonic acid (HCO_3^- / H_2CO_3) is 20:1.

ii. Phosphate buffer system:

- It is not important extracellular fluid buffer.
- It plays a major role in buffering renal tubular fluid and intracellular fluids.
- The phosphate buffer system has a PK of 6.8.
- The main elements of the phosphate buffer system are $H_2PO_4^-$ and HPO_4^{--}.
- At a plasma PH of 7.4 the ratio of HPO_4^{--} and $H_2PO_4^-$ is 4:1.
- Its concentration in extracellular fluid is low, only about 8% of concentration of the bicarbonate buffer.

iii. Protein buffer system:

- Plasma proteins play a limited role in extracellular buffer system while intracellular proteins play an important role in the total buffer response of the body.

Isohydric Principle:

- All buffers in a common solution are in equilibrium with the same H^+ concentration. Therefore, whenever there is a change in H^+ concentration in the extracellular fluid. The balance of all the buffer systems changes at the same time. This phenomenon is called the Isohydric principle.

Extracellular factors that increase or decrease H^+ secretion and HCO_3 reabsorption the renal tubules:

Increase H+ Secretion and HCO3 reabsorption	Decrease H+ Secretion and HCO3 reabsorptio
Increase H^+ and decrease HCO_3	Decrease H^+ and increase HCO_3
Decrease in extracellular fluid volume	Increase in extracellular fluid volume
Increase in partial pressure of CO_2	Decrease in partial pressure of CO_2
Increase Angiotensin II	Decrease Angiotensin II
Increase Aldosterone	Decrease Aldosterone
Hypokalemia	Hyperkalemia

Respiratory Acidosis:

- It results from decrease ventilation and increase partial pressure of CO_2.

Causes:-

- Conditions that cause respiratory acidosis are,
- Asthma
- Emphysema
- Pneumonia
- Cardiac arrest
- Administration of respiratory depressant toxic drugs. e.g: Morphine

Compensatory Mechanism:-

- Increase in renal bicarbonate reabsorption.

Respiratory Alkalosis:-

- It results from increased ventilation and decreased partial pressure of CO_2.

Causes:-

- Conditions that cause respiratory alkalosis are,
- Hyperventilation (Anxiety, fever)
- Hot baths
- High altitudes
- Working at high temperature
- Salicylate poisoning.

Compensatory mechanism:-

- Decrease in renal bicarbonate reabsorption

Metabolic Acidosis:-

- It results from decreased extracellular fluid bicarbonate (HCO_3^-) concentration.
- It refers to all other types of acidosis besides those caused by excess CO_2 in the body

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Causes:-

- Conditions that cause metabolic acidosis are:
- Diabetes mellitus
- Therapeutic administration of HCL
- Renal failure
- Severe diarrhea

Compensatory Mechanism:-

- Hyperventilation which decreases partial pressure of CO_2.

Metabolic Alkalosis:-

- It results from increased extracellular fluid bicarbonate (HCO_3^-) concentration.

Causes:

- Conditions that cause metabolic alkalosis are,
- Administration of diuretics
- Excess aldosterone
- Vomiting of Gastric Contents
- Ingestion of Alkaline drugs.

Compensatory Mechanism:-

- Hypoventilation which increases partial pressure of CO_2 and increases renal HCO_3^- excretion, which helps compensate for the initial rise in extracellular fluid HCO_3^- concentration.

Anion Gap:-

- It is the difference between unmeasured anions and unmeasured cations.
- It is estimated as:
- Anion gap= $[Na^+] - [HCO_3^-] - [Cl^-]$

$$= 144 - 24 - 108 = 12 \text{ mEq/L.}$$

- The normal value of plasma anion gap is 12 mEq/L and ranges between 8 and 16 mEq/L.
- It is used in the diagnosis of different causes of metabolic acidosis.
- The anion gap will increase if unmeasured anions rise or if unmeasured cations fall.
- The most important unmeasured cations include calcium, magnesium and potassium, and the major unmeasured anions are albumin, phosphate, sulfate and other organic anions.
- In metabolic acidosis, plasma HCO_3^- concentration is reduced. If plasma sodium concentration in unchanged, the concentration of anions either chloride or an unmeasured anion must increase to maintain electro neutrality.

Hyper-chloremic metabolic acidosis or normal anion gap acidosis:-

- If plasma chloride ion increases in proportion to the fall in plasma HCO_3^-, the anion gap remain normal. This is called hyper-cholremic metabolic acidosis or normal anion acidosis.

Metabolic acidosis with increased anion gap:-

- If the decrease in plasma HCO_3^- is not accompanied by increased Chloride ion, there be increased levels of unmeasured anions to replace HCO_3^-. This is called metabolic acid with increased anion gap.

Metabolic acidosis associated with normal & increased plasma anion gap

Increased Anion Gap	Normal Anion Gap
Diabetic ketoacidosis	Diarrhea
Renal failure	Pancreatitis
Methanol toxicity	Intestinal fistula
Alcoholic ketoacidosis	Renal tubular Acidosis
Paracetamol toxicity	Acetazolamide
Lactic acidosis	
Ethylene glycol poisoning	
Salicylate toxicity	

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Diuretics:-

- Any substance that increases the rate of urine volume output.

Uses of Diuretics:-

- To reduce extracellular fluid volume, especially in diseases associated with edema & hypertension.

Types of diuretics:-

Loop Diuretics:-

- Furosemide, Ethacrynic acid and bumetanide are loop diuretics that decrease active reabsorption in the thick ascending limb of the loop of henle by blocking the 1-sodium, 2-chloride, 1-potassium co-transporter located in the luminal membrane of the epithelial cells.

Osmotic diuretics:-

- Mannitol is osmotic diuretic that inhibit water and solute reabsorption by increasing osmolarity of tubular fluid mainly in proximal tubules.

Thiazide diuretics:-

- Thiazide diuretics such as chlorothiazide inhibit Na^+- Cl^- co-transport in luminal membrane of early distal tubules.
  Note: Thiazide diuretics are the only diuretics that cause hypercalcemia.

Carbonic anhydrase inhibitor:

- Carbonic anhydrase inhibitors such as acetazolamide inhibit H^+ secretion & HCO_3^- reabsorption, which reduces Na^+ reabsorption in proximal tubules. A disadvantage of the carbonic anhydrase inhibitors is that they cause some degree of acidosis because of excessive loss of HCO_3^- in the urine.

Potassium sparing diuretics:-

- Aldosterone antagonists or mineralocorticoid receptor antagonists such as spironolactone and eplerenone inhibit action of aldosterone on tubular receptor, decrease Na^+ reabsorption and K^+ secretion in collecting tubules. Aldosterone antagonists are potassium sparing diuretics.
- Sodium channel blockers such as triamterene & amiloride decrease Na^+ reabsorption and decrease K^+ secretion in collecting tubules. Sodium channel blockers are also potassium sparing diuretics.

Acute kidney injury:-

- Also called acute renal failure.
- An abrupt loss of kidney function occurs within a few days.
- May recover nearly normal kidney function.

Causes of acute kidney injury:-

- Pre-renal acute kidney injury resulting from decreased blood supply to the kidneys.
- Intra-renal acute kidney injury resulting from abnormalities within the kidney including those that affect the blood vessels, glomeruli or tubules.
- Post-renal acute kidney injury resulting from obstruction of the urinary collecting anywhere from the calyces to the outflow from the bladder.

Oliguria:

- Oliguria refers to diminished urine output.

Anuria:

- Anuria is complete cessation of urine output.

Glomerulonephritis:-

- A type of intra-renal acute kidney injury results from an abnormal immune reaction damages the glomeruli.

Causes:

- Caused by certain types of group A beta streptococci infection.
- It is not the infection that damages the kidneys. Instead the antibodies and antigen with each other to form an insoluble immune complex that becomes entrapped in glomeruli.

Symptoms:

- Many of the glomeruli become blocked by this inflammatory reaction.
- Those not blocked become excessively permeable, allowing both protein and red cells to leak into urine.

Chronic kidney disease:-

- There is progressive loss of function of more and more nephrons that gradually decre overall kidney function and persist for at least three months.
- Irreversible loss of large number of functioning nephrons occurs.

Causes:

- Occur b/c of disorders of the blood vessels, glomeruli, tubules, renal interstitium and urinary tract.

End-stage renal disease:-

- When an initial insult to the kidney leads to progressive deterioration of kidney fu and further loss of nephrons to the point where the person must receive dialysis trea or undergo transplantation with a functional kidney to survive. This condition is calle stage renal disease.

Pyelonephritis:-

- It is renal interstitial injury caused by bacterial infection.

Causes:-

- The infection can result from different types of bacteria but especially from E- coli that originate from fecal contamination of the urinary tract.

Isosthenuria:-

- It is the inability of the kidney to concentrate or dilute urine.
- It develops when 67% of nephrons become non-functional.

Total kidney excretion and excretion per nephron in kidney diseases:

	Normal	75% loss of Nephrons
Number of Nephrons	2,000,000	500,000
Total GER (ml/min)	125	40
Single Nephron GER (ml/min)	62.5	80
Volume excreted for all nephrons (ml/min)	1.5	1.5
Volume excreted per nephron (ml/min)	0.75	3.0

Uremia:-

- It is a condition of having high levels of urea in the blood.

Azotemia:-

- It is a condition characterized by abnormally high levels of nitrogen containing compounds such as urea, uric acid, creatinine and various body waste compounds in the blood.

Fanconi's syndrome:-

- Generalized reabsorptive defect of the renal tubules.
- Associated with increased urinary excretion of amino acids, Glucose and Phosphate.

Barters syndrome:-

- Rare autosomal recessive disorder.
- Caused by impaired function of the 1-Sodium, 2-Cholride, 1-Potassium co-transporter.
- Results in increased excretion of water, sodium, chloride and potassium.
- Also leads to hypokalemia and metabolic alkalosis.

Gitelman's Syndrome:-

- Autosomal recessive disorder of the thiazide sensitive sodium-chloride co-transporter in the distal tubules.
- Results in decreased sodium chloride reabsorption in the distal tubules.

Liddle's syndrome:-

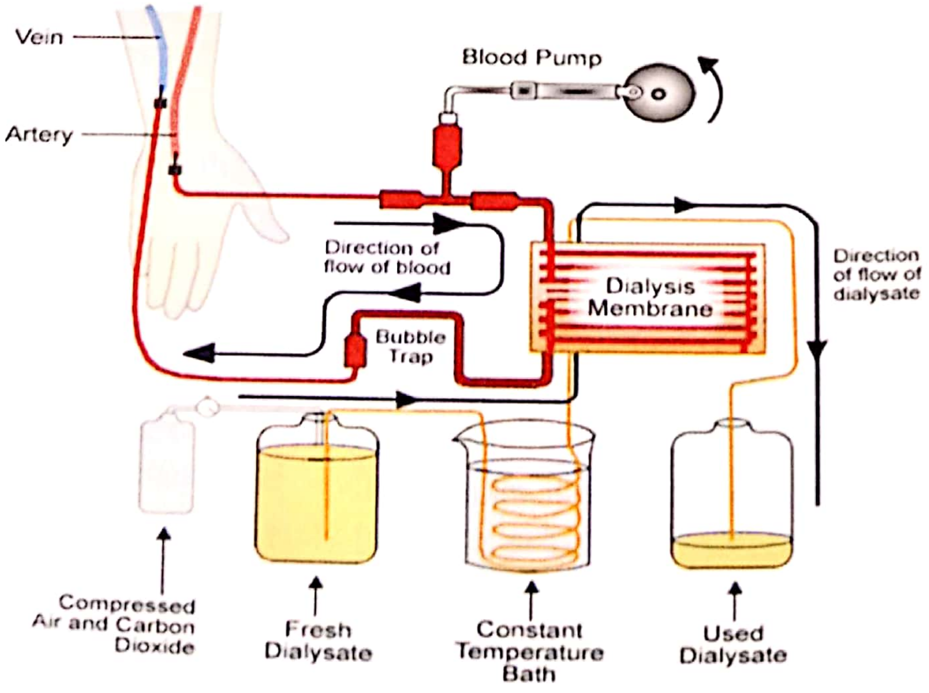
- Autosomal dominant disorder resulting from various mutations in the amiloride-sensitiv epithelial sodium channel in the distal and collecting tubules.
- These mutations cause excessive activity of the epithelial sodium channels, resulting i increased reabsorption of sodium and water.
- Have decreased level of aldosterone as a result of sodium retention and compensato decrease in renin secretion and angiotensin II levels which in turn decrease adrena secretion of Aldosterone.
- Treated with diuretic amiloride, which blocks the excessive sodium channel activity.

Dialysis:-

- A procedure used to remove waste products and excess fluid from the blood when th kidneys stop working properly.

Dialyzer:

- A machine used during dialysis.
- In dialyzer thin membrane of cellophane is used.
- Total blood in artificial kidney at any one time is less than 500 ml and the total diffusio surface area is between 0.6 & 2.5 square meters.
- In dialyzer anticoagulant heparin is used.
- There is no phosphate, urate, urea, sulfate or creatinine in the dialyzing fluid.
- Most artificial kidneys can clear urea from the plasma at a rate of 100 to 225 ml/min, whi urea clearance of both normal kidney is 70 ml/min.
- The artificial kidney is used for only 4 to 6 hours per day, three times a week.


Vein
Artery
Blood Pump
Direction of flow of blood
Dialysis Membrane
Bubble Trap
Direction of flow of dialysate
Compressed Air and Carbon Dioxide
Fresh Dialysate
Constant Temperature Bath
Used Dialysate

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Part-II

SENSORY PHYSIOLOGY

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Organization of the nervous system:

- The central nervous system contains more than 100 billion neurons.
- More than 99% of all sensory information is discarded by the brain as irrelevant a unimportant. However, when important sensory information excites the mind, i immediately channeled into proper integrative and motor regions of the brain to ca desired responses. This channeling and processing of information is called the integra function of the neurons system.

Synapse:-

- The synapse is the junction point from one neuron to the next.
- Synapses determine the directions that the neurons signals will spread through the nervo system.
- The storage of information is the process we call memory, and this too is a function of th synapses.

Types of synapses:-

- There are two types of synapses,

Chemical Synapses:-

- At a chemical synapse an action potential triggers the presynaptic neuron to releas neurotransmitters.
- These molecules bind to receptors on the postsynaptic neuron and make it more or les likely to fire an action potential.
- In chemical synapses synaptic cleft is 200-300A°.
- Chemical synapses always transmit the signals in one direction.
- The neuron that secretes the neurotransmitter is called presynaptic neuron.
- The neuron on which the transmitter acts is called postsynaptic neuron.
- The equality of neurotransmitter release from terminal into synaptic cleft is directly relate to the number of calcium ions that enter the presynaptic terminal.

Electrical Synapses:-

- It is an electrically conductive junction between two cells formed by arrays of gap junctio channels.
- Electrical synapses have intercellular gap of 20-40A°.
- Electrical synapses transmit signals in bi-direction.

Mechanism of neurotransmitter release from presynaptic terminal:-

- The presynaptic membrane contains large numbers of voltage gated calcium channels.
- When an action potential depolarizer the presynaptic membrane, calcium channels ope and calcium ions enter into presynaptic terminal.
- Calcium ions entry cause release of neurotransmitter from terminal into synaptic cleft.
- Neurotransmitter then act on postsynaptic membrane.

Presynaptic terminal:-

- The presynaptic terminal has two internal structures important to the excitatory or inhibitory function of the synapse, the transmitter vesicles and the mitochondria.
- The transmitter vesicles contain the neurotransmitter that when released into the synaptic cleft, either excites or inhibits the postsynaptic neuron.
- It excites the postsynaptic neuron if the neuronal membrane contains excitatory receptors.
- It inhibits the neuron if the membrane contains inhibitory receptors.
- The mitochondria provide ATP which in turn supplies the energy for synthesizing new transmitter substance.

Types of neurotransmitter Receptors:-

Inotropic receptors:-

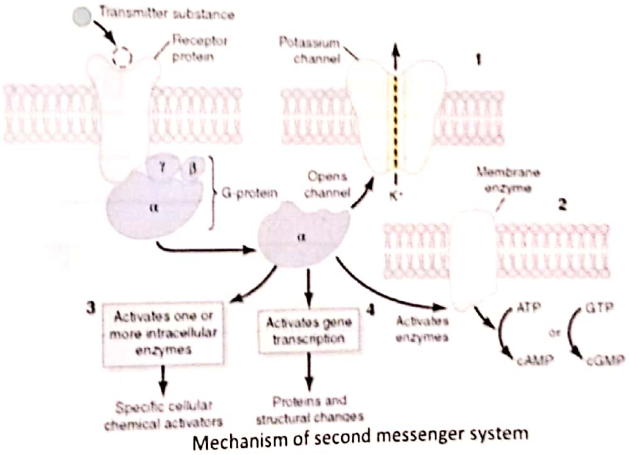
- Neurotransmitter receptors that directly gate ion channels are called inotropic receptors.

Metabotropic Receptors:-

- Those receptors that act through second messenger systems are called metabotropic receptors.

G-Protein:-

- G-Protein is trimeric molecule consists of α, β and γ components.
- Alpha (α) component is the activator portion of the G-Protein because GTP binds to alpha component.
- Inactivation of the G-Protein occurs when the GTP bound to the α-subunit is hydrolyzed to GDP.


Transmitter substance
Receptor protein
Potassium channel
1
γ
β
α
G-protein
Opens channel
K⁺
Membrane enzyme
2
α
3
Activates one or more intracellular enzymes
Activates gene transcription
4
Activates enzymes
ATP
GTP
or
cAMP
cGMP
Specific cellular chemical activators
Proteins and structural changes

Mechanism of second messenger system

Neurotransmitters:-

- Gamma-Amino Butyric Acid (GABA) is inhibitory neurotransmitter in the brain.
- Glycine is inhibiting neurotransmitter in the spinal cord.
- Acetylcholine is synthesized in the presynaptic terminal from acetyl coenzyme A and Choline in the presence of the Enzyme choline acetyltransferase. In the synaptic cleft acetylcholine is rapidly split again to acetate and choline by the enzyme cholinesterase, which is present in the proteoglycan reticulum that fills the space of the synaptic cleft.
- Acetylcholine and norepinephrine both act as excitatory and inhibitory neurotransmitters.
- Glutamate, Aspartate, nitric oxide, carbon mono-oxide and substance p act as excitatory neurotransmitters.
- Dopamine, glycine, GABA and serotonin act as inhibitory neurotransmitters.

Small molecules, rapidly acting transmitters:-

- In most cases, the small molecule types of transmitters are synthesized in the cytosol of t presynaptic terminals and are absorbed by means of active transport into the transmi vesicles.
- Nitric oxide is an exception; it is not preformed and stored in vesicles in the presynap terminal as are other transmitters. Instead it is synthesized almost instantly as needed a then defuses out of the presynaptic terminals over a period of seconds rather than be released in vesicular packets.
- In the postsynaptic neuron, It usually does not greatly alter the membrane potential b instead changes intracellular metabolic functions that modify neuronal excitability f seconds, minutes or even longer.

Neuropeptides:-

- Neuropeptides are not synthesized in the cytosol of the presynaptic terminals.
- Instead, they are synthesized as integral parts of large protein molecules by ribosomes the neuronal cell body.
- Once released the vesicle is autolyzed and is not reused, because of this much smal quantities of neuropeptides are usually released.
- The neuropeptides are more potent than small molecule transmitter and often cause mu more prolonged actions.

Small molecules, rapidly acting Transmitters:-

Class I	Class III: Amino Acids
Acetylcholine	GABA
Class II: The Amines	Glycine
Norepinephrine	Glutamate
Epinephrine	Aspartate
Dopamine	Class IV:
Serotonin	Nitric oxide
Histamine	

Neuropeptides, slowly acting Transmitters:

Hypothalamic- Releasing Hormones:	Pituitary Peptides
Thyrotropin releasing hormone	β-Endrophin
Luteinizing hormone releasing hormone	Prolactin
Somatostatin (Growth hormone inhibitory factor)	Vasopressin, Oxytocin

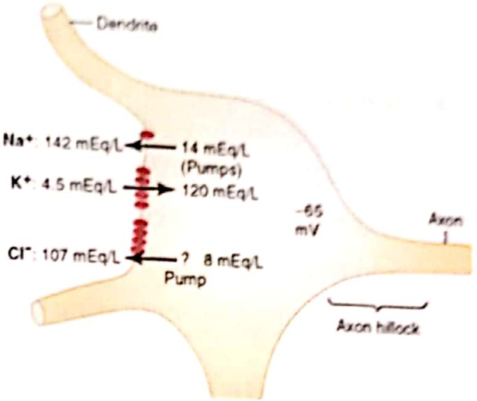
Concentration differences of ions across the neuronal somal membrane

Ions	Extracellular fluid	Inside the neuron
Na^+	142 mEq/L	14 mEq/L
K^+	4.5 mEq/L	120 mEq/L
Cl^-	107 mEq/L	8 mEq/L

Nernst Potential:

- A potential that exactly opposes movement of an ion across a membrane is called Nernst potential for that ion.
- At Nernst potential of an ion there is no net flow of that particular ion from one side of the membrane to the other side.
- Nernst potential can be represented as,

$$\text{Nernst Potential (mv)} = \pm\, 61 \times \log\left[\frac{\textit{concentration inside}}{\textit{concentratoin outside}}\right]$$



Distribution of Sodium Potassium and chloride ions across the neuronal somal membrane

- Nernst potential for sodium is + 61 millivolts.
- Nernst potential for potassium is -86 millivolts.
- Nernst potential for chloride ion is -70 millivolts.

Generation of action potential in the initial segment of axon:-

- Action potential does not begin adjacent of excitatory synapse, instead it begins in the initial segment of axon because the membrane of the initial segment of the axon leaving the neuron has seven times as great a concentration of voltage-gated sodium channels as does the soma, and therefore can generate an action potential with much greater ease than can the soma.

Note:

- Resting membrane potential of soma of spinal motor neuron is about -65 millivolts whereas resting membrane potential in large peripheral nerve fibre and in skeletal muscle fibre is -90 millivolts

EPSP and IPSP:-

- An increase in positive voltage above the normal resting membrane potential that is to a less negative value is called excitatory post synaptic potential, whereas an increase in negativity beyond the normal resting membrane potential is called an inhibitory postsynaptic potential.
- Excitatory postsynaptic potential and inhibitory post synaptic potential dies away is about 15 milliseconds.

Presynaptic inhibition:-

- It refers to mechanisms that suppress release of neurotransmitters from axon terminals.
- It involves binding of chemical messengers to inhibitory receptors at transmitter release sites on the axon.

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Spatial Summation:-

- The effect of summing simultaneous postsynaptic potentials by activating multipl terminals on widely spaced areas of neuronal membrane is called spatial summation.
- It is obtained by using increasing number of parallel fibers.

Temporal summation:-

- The successive discharges from a single synaptic terminal, if they occur rapidly enough can add to one another, this type of summation is called temporal summation.
- It is obtained by increasing the frequency of nerve impulses in each fiber.

Electronic conduction in dendrites:-

- It means direct spread of electrical current by ion conduction in the fluids of the dendrites but without generation of action potentials.
- The decrease in membrane potential as it spreads electronically along dendrites toward the soma is called decremental conduction.
- The farther the excitatory synapse is from the soma of the neuron, the greater will be the decrement and the lesser will be the excitatory signal reaching the soma.

Fatigue of synaptic transmission:-

- When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the postsynaptic neuron is at first very great, but the firing rate becomes progressively less in succeeding milliseconds or seconds. This phenomenon is called fatigue of synaptic transmission.
- The mechanism of fatigue is mainly exhaustion or partial exhaustion of the stores of transmitter substance in the presynaptic terminals.
- The development of fatigue is a protective mechanism against excess neuronal activity, because when areas of the nervous system become overexcited, fatigue causes them to lose this excess excitability after a while.

Effect of alkalosis on synaptic transmission:-

- Alkalosis greatly increases neuronal excitability.
- For example, a rise in arterial blood pH from the 7.4 normal to 7.8 often causes cerebra epileptic seizures because of increased excitability of cerebral neurons.

Effect of acidosis of synaptic transmission:-

- Acidosis greatly depresses neuronal activity.
- For example a fall in pH from 7.4 to below 7.0 usually causes a comatose state.

Effect of drugs on synaptic transmission:-

- Caffeine, theophylline and theobromine which are found in coffee, tea and coco respectively all increase neuronal excitability by reducing the threshold for excitation o neurons.

- Strychnine increase excitability of neurons by inhibiting the action of some normally inhibitory transmitter substances, especially the inhibitory effect of glycine in the spinal cord.
- Most anesthetics increase the neuronal membrane threshold for excitation and thereby decrease synaptic transmission at many points in the nervous system.

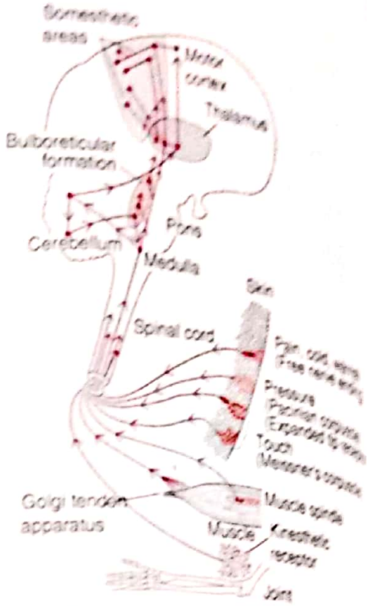
Synaptic Delay:-

- The minimal period of time required for all the events to take place, during transmission of a neuronal signal from presynaptic neuron to a post synaptic neuron, even when large numbers of excitatory synapses are stimulated simultaneously is called synaptic delay.
- Synaptic delay is about 0.5 milliseconds.

Receptors:

- It isan organ or cell able to respond to light, heat or other external stimulus and transm signal to a sensory nerve.
- Each type of receptor is highly sensitive to one type of stimulus for which it is designed an yet is almost non responsive to other types of sensory stimuli.

Types of Sensory Receptors:-



Somatosensory axis of the nervous syste

- There are five basic types of sensory receptors,

Mechanoreceptors:

- Detect mechanical compression or stretching of the issues.

Thermo-receptors:

- Detect change in temperature.

Nociceptors or pain receptors:

- Detect physical or chemical damage occurring in tissues.

Electromagnetic receptors:

- Detect light on the retina of the eye.

Chemoreceptors:

- Detect taste in the mouth, smell in the nose and osmolarity of the body fluids.

Modality of sensation:-

- Each of the principal types of sensation that we can experience-pain, touch, sight, sou and so forth is called a modality of sensation.

The "labeled line" principal:-

- The specificity of nerve fibers for transmitting only one modality of sensation is called t labeled line principal.

Receptor potentials:

- *All sensory receptors have one feature in common, whatever the type of stimulus t excites the receptor, its immediate effect is to change the membrane electrical potentia the receptor. This change in potential is called a receptor potential.*
- *The maximum amplitude of most sensory receptor potentials is about 100 millivolts.*
- *The relation between stimulus intensity and the receptors potentials is that the amplit of receptor potential increases rapidly at first and then progressively less rapidly at hi stimulus strength.*

Adaption of receptors:-

- When a continues sensory stimulus is applied, the receptor responds at a high impulse rate at first and then at a progressively slower rate until finally the rate of action potentials decreases to very few or often to none at all.
- Pacinian corpuscle adapts very rapidly, hair receptors adapt within a second and muscle spindle receptors adapt slowly.
- The chemoreceptors and pain receptors probably never adapt completely.

Slowly Adapting receptors:-

- Slowly adapting receptors continue to transmit impulses to the brain as long as the stimulus is present.
- Because the slowly adapting receptors can continue to transmit information for many hours or even days, they are called tonic receptors.
- **Example:**
- Muscle spindles and Golgi tendon Apparatus, receptors of the macula in vestibular apparatus, pain receptors, baroreceptors of the arterial tree and chemoreceptors of the carotid and aortic bodies.

Rapidly Adapting receptors:-

- Receptors that adapt rapidly cannot be used to transmit a continuous signal because they are stimulated only when the stimulus strength changes.
- Therefore these receptors are called rate receptors, movement receptors or phasic receptor.

Example: Pacinian Corpuscles

Range of diameter and velocities of nerve fibers:-

- The range of diameter of nerve fibers is between 0.5 and 20 micrometers.
- The range of conducting velocities is between 0.5 and 120 m/s.

General Classification of nerve fibers:-

Type of Nerve Fiber	Example	Myelination
A alpha (Aα)	Large α motors neurons of skeletal muscle (Extrafusal to muscle spindle)	Yes
A beta (Aβ)	Touch, Pressure	Yes
A gamma (Aγ)	γ-motor neurons to muscle Spindles (Intrafusal Fibres)	Yes
A delta (Aδ)	Touch, pressure, temperature, fast pain	Yes
B	Preganglionic autonomic nerves	Yes
C	Slow pain, postganglionic autonomic nerves	No

Numerical classification of sensory fibers:-

Numerical classification	Diameter	Fiber Type	Example	Myelinatio
Ia	17µm	Aα	Muscle Spindle afferents	Yes
Ib	16µm	Aα	Golgi tendon organ afferents	Yes
II	8µm	Aβ & Aγ	Secondary afferents of muscle Spindle, touch & Pressure	Yes
III	3µm	Aδ	Touch, Pressure, fast pain, Temperature	Yes
IV	0.5-2µm	C	Pain, Temperature	NO

Divergence of signals passing through neuronal pools:-

- It is important for weak signals entering a neuronal pool to excite far greater number nerve fibers leaving the pool. This phenomenon is called divergence.

Types of divergence:-

- There are two types of divergence occur,

Amplifying divergence:

- Input signal spreads to an increasing number of neurons as it passes through succes orders of neurons in its path.
- It is characteristic of the corticospinal pathway in its control of skeletal muscles.

Divergence into multiple tracts:

- In this case, the signal is transmitted in two directions from the pool.

onvergence of signals:

t means signals from multiple inputs uniting to excite a signal neuron.

Reciprocal inhibition:-

- It is characteristic for controlling all antagonistic pairs of muscles.

After-discharge:-

- A Signal entering a pool cause a prolonged output discharge called after discharge, las few milliseconds to as long as many minutes after the incoming signal is over.

Reverberatory circuit:-

- It is caused by positive feedback within the neuronal circuit that feeds back to re-excite input of the same circuit. A facilitatory signal enhances the intensity and frequen reverberation whereas an inhibitory signal depresses the reverberation.

Somatic senses:-

- These senses collect sensory information from all over the body.
- These senses include tactile, position, pain and thermal senses.
- On other side the special senses include vision, hearing, smell, taste and equilibrium.

Classification of somatic senses:-

- It can be classified into three types.

Mechanoreceptive senses:

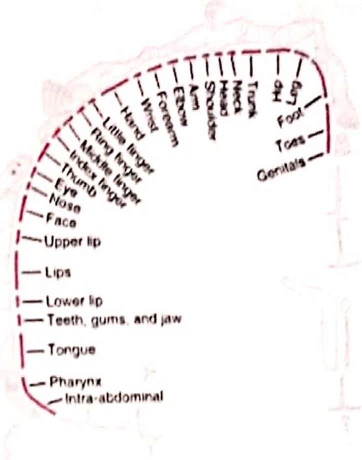
- It includes both tactile and position sensations.
- The tactile senses include touch, pressure, Vibration and tickle senses.
- The position senses include static position and rate of movement senses.

Thermoreceptive senses:

- Detect heat and cold.

Pain Senses:

- Activated by factors that damage the tissues.



Somatosensory cortex

Other classification of somatic sensations:-

Exteroceptive sensations:

- Those from the surface of the body.

Proprioceptive Sensations:

- Those relating to the physical state of the body including position sensations, tendon and muscle sensations, pressure sensation from the bottom of the feet and even sensation of equilibrium which is often considered a special sensation.

Visceral Sensations:

- Those from the viscera of the body, specifically sensation from internal organs.

Deep Sensations:

- Those come from deep tissues such as from fasciae, muscles and bone.

Tactile Receptors:-

- There are six different types of tactile receptors,

Free nerve Endings:-

- Sensitive to touch and pressure.

Meissen's Corpuscle:-

- An elongated encapsulated nerve ending of a large (type Aβ) myelinated sensory fiber.
- Particularly sensitive to touch and low frequency vibration.
- Present in the non-hairy parts of the skin such as finger and lips.
- Adapt in a fraction of a second after they are stimulated.

Merkel's discs:-

- Present in fingertips and the hairy parts of the skin.
- Sensitive to touch.
- Differ from Meissener's corpuscles in that they transmit an initially strong but par adapting signal and then continuously a weaker signal that adapts slowly.
- Responsible for giving steady state signals that allow one to determine continuous touc objects against the skin.
- Grouped together in a receptor organ called the Iggo dome receptors.
- Group of Merkel disc is innervated by a single large myelinated nerve fiber (Type Aβ).

Hair End Organ:-

- Each hair and its basal nerve fiber called the hair end-organ are also touch receptors.
- Adapts readily and detects mainly movement of objects on the surface of the body or i contact with the body.

Ruffini's Endings:-

- Multibranched, encapsulated endings, adapt very slowly and are important for sig continuous states of deformation of the tissues.
- Also found in joint capsules and signal the degree of joint rotation.

Pacinain capsules:-

- An encapsulated nerve ending acts as a receptor for pressure and vibration.
- Stimulated only by rapid local compression of the tissues.
- Adapt rapidly.

Transmission of tactile signals in peripheral nerve fibers:-

- All specialized sensory receptors such as meissner's corpuscles, Iggo dome receptors receptor, pacinian corpuscles and Ruffini's endings transmit their signal in type Aβ fibers that have transmission velocity 30 to 70 m/sec.
- Free nerve endings tactile receptors transmit signals by way of the small type Aδ myli fibers that have velocity of 5 to 30 m/sec.
- Some free nerve endings transmit by way of type C fibers at velocity of 1-2 m/sec.
- The tickle, itch and slow type of pain sensation are transmitted by very small type C fibe

Detection of vibration:-

- All tactile receptors are involved in detection of vibration of different frequencies range.
- Pacinian corpuscles detect vibrations from 30 to 800 cycles/sec and transmit their signals over type Aβ nerve fibers which can transmit as many as 1000 impulses per second.
- Low frequency vibrations from 2 - 80 cycles/sec stimulate meissner's corpuscles.

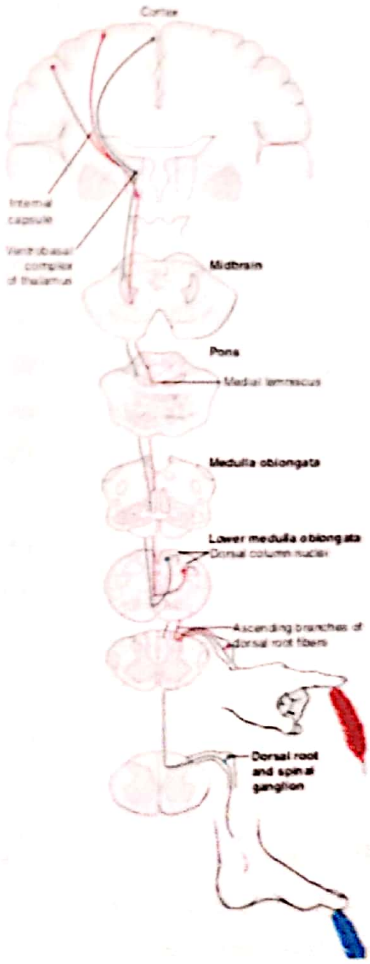
Pathways for transmitting somatic signals into CNS:-

- All sensory signals from the somatic segments of the body enter the spinal cord through the dorsal roots of the spinal nerves.
- From the entry point into the cord and then to the brain, the sensory signals are carried through one of the two sensory pathways.
- The dorsal column- medial lemniscal system.
- The Anterolateral system.

The dorsal column-medial lemniscal system:

Pathway:-

- Nerve fibers entering the dorsal column of spinal cord pass into the dorsal medulla, synapse in the dorsal column nuclei (cuneate and gracile nuclei).
- From there second order neurons decussate to the opposite side of the brain stem and continue upward through the medial lemnisci to the thalamus.
- Through the brain stem, each medial lemniscus is joined by additional fibers from the sensory nuclei of the trigeminal nerve, these fibers sub serve the same sensory functions for the head that the dorsal column fibers sub serve for the body.
- In the thalamus the medial lemniscal fibers terminate in the thalamic sensory relay area called the ventrobasal complex.
- From the ventrobal complex, third order nerve fibers project mainly to the postcentral gyrus of the cerebral cortex, which is called somatic sensory area I.
- These fibers also project to a smaller area in the lateral parietal cortex called somatic sensory area II.



The dorsal column medial lemeniscal pathway

Characteristics:-

- Composed of large, myelinated fibers that transmit signals at velocities of 30 - 110 m/sec.
- Has a high degree of spatial orientation of the nerve fibers with respect to their origin. Sensory signal that must be transmitted rapidly with spatial fidelity is transmitted in this system.

- Transmit discriminative touch, vibratory sensations, position sensation from the joints, sensations that signal movement against the skin and pressure sensations.
- The medial lemnisci decussate in the medulla, the left side of the body is represent in the right side of the thalamus and the right side of the body is represented in the left side of the thalamus.
- Decussation of fiber occurs in the medulla.
- At each synaptic stage divergence occurs.

Lesion of the dorsal column-medial lemniscal pathway:-

- Lesion below the decussation point results in loss of vibration, discriminative touch and proprioception on ipsilateral side of the body to the lesion.
- Lesion above the decussation point results in loss of vibration, discriminative touch and proprioception on contralateral side of the body to the lesion.

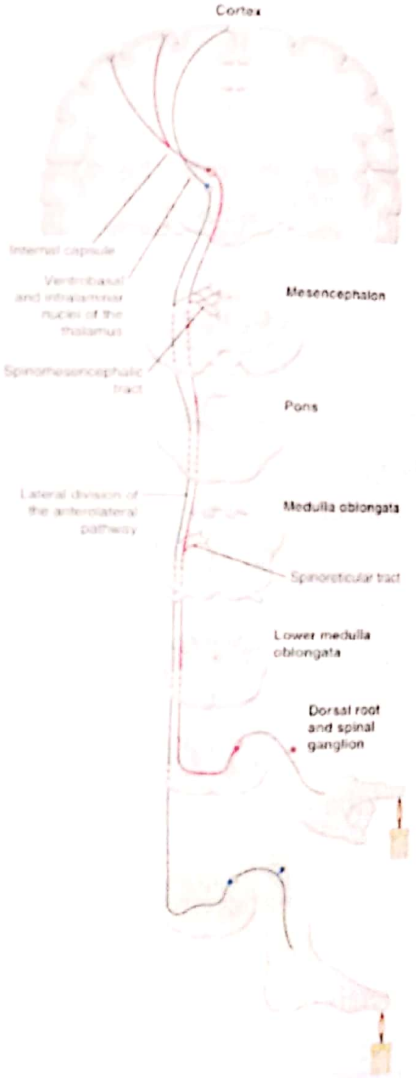
Anterolateral system:-

Pathway:-

- Spinal card anterolateral fibers originate in dorsal horn laminae I, IV, V & VI.
- These laminae are present where dorsal root sensory fibers terminate after entering cord.
- Anterolateral fibers cross in the anterior commissure of the cord to the opposite anterior and lateral white columns and turn upward toward the brain by way of the anterior spinothalamic and lateral spinothalamic tracts.
- The signals are transmitted to the ventrobosal complex, terminating in some of the same thalamic nuclei where the dorsal column tactile signals terminate.
- From here, the signals are transmitted to the somatosensory cortex.

Characteristics:-

- Composed of smaller myelinated fibers that transmit signals at velocity of 8 - 40 m/sec.
- Has less spatial orientation, and the degree of spatial localization of signals is poor. Sensory signals which does not need to be transmitted rapidly or with great spatial fidelity is transmitted in anterolateral system.
- The anterolateral system transmits a broad spectrum of sensory modalities such as pain, warmth, cold, crude tactile sensations and sexual sensations.


Cortex
Internal capsule
Ventrobasal and intralaminar nuclei of the thalamus
Mesencephalon
Spinomesencephalic tract
Pons
Lateral division of the anterolateral pathway
Medulla oblongata
Spinoreticular tract
Lower medulla oblongata
Dorsal root and spinal ganglion

Anterolateral pathway

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- Decussate of fibers occur in the anterior commissure of spinal cord.

Lesion of the anterolateral pathway:-

- Lesion of the anterolateral pathway results in loss of pain, temperature and crude touch on contralateral side of the body below the level of lesion.

Somatosensory cortex:-

- Based on histological structural difference Brodmann divide cerebral cortex into 50 distinct areas called Brodman's areas.
- Sensory signals from all modalities of sensation terminate in the cerebral cortex immediately posterior to the central sulcus called sensory cortex.
- Visual signals terminate in the occipital lobe, and auditory signals terminate in the temporal lobe.
- The portion of the cerebral cortex anterior to the central sulcus and constituting the posterior half of the frontal lobe is called the motor cortex and is devoted to control of muscle contractions and body movements.
- Cerebral cortex control contralateral side of the body.
- Some areas of the body are represented by large areas in the somatic cortex-the lips the greatest of all.
- The sizes of these areas are directly proportional to the number of specialized sensory receptors in each peripheral area of the body.
- The head is represented in the most lateral portion of sensory cortex and the lower part of the body is represented medially.

Somatosensory Area I:-

- Somatosensory area I lie behind the central sulcus, located in the post central gyrus of the human cerebral cortex (in Brodman's areas 3, 1 & 2).

Lesion of somatosensory area I:

- Bilateral lesion of somatosensory area I causes loss of the following types of sensory judgment,
- The person is unable to localize discretely the different sensations in the different parts of the body. However he or she can localize these sensations crudely.
- The person is unable to judge critical degrees of pressure against the body.
- The person is unable to judge the weights of objects.
- The person is unable to judge shapes or forms of objects, this condition is called astereognosis.
- The person is unable to judge texture of materials.
- In lesion of somatosensory area I, appreciation of pain and temperature is still preserved both in quality and intensity. However the sensations are poorly localized.

Somatosensory area II:

- Brodman's areas 5 and 7 of the cerebral cortex, located in the parietal cortex behind somatosensory area I play important roles in deciphering deeper meanings of the sensory information in the somatosensory areas.
- Also called somatosensory association areas.

Amorphosynthesis:

- When the somatosensory association area is removed on one side of the brain, the person loses the ability to recognize complex objects and complex forms felt on the opposite of the body.
- The person also forgets to use the other side for motor functions as well.
- When feeling objects tends to recognize only one side of the object and forgets other side.
- This complex sensory deficit is called amorphosynthesis.

Layers of somatosensory cortex:

- Cerebral cortex consists of six layers of neurons.
- At layer IV, the input sensory signals first enter the cortex and excites neuronal layer IV first, the signal then spreads toward the surface and deeper layers of cortex.
- Layers I and II receive diffuse input signals from lower brain centers that facilitate specific regions of the cortex.
- The neurons in layers II and III send axons to related portions of the cerebral cortex on the opposite side of the brain through the corpus callosum.
- The neurons in layers V and VI send axons to the deeper parts of the nervous system.

Two point discrimination:

- It is used to test tactile discrimination to determine a person so called "two point" discrimination ability.
- In this test two needles are pressed lightly against the skin at the same time and the person determines whether one point or two points is/are felt.
- On the tips of fingers, a person can normally distinguish two separate points even when the needles are as close as 1 to 2 mm.

Corticofugal signals:

- In addition to signals transmitted from the periphery to the brain, corticofugal signals are transmitted in the backward direction from the cerebral cortex to the lower sensory relay stations of the medulla, thalamus and spinal cord.
- These signals control the intensity of sensitivity of the sensory input.
- These signals are entirely inhibitory, when sensory input intensity becomes too great, the corticofugal signals automatically decrease transmission in the relay nuclei.
- This principle of corticofugal sensory control is used by all sensory systems.

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First, second and third order neurons:

- The ascending pathway to consciousness consists of these three order neurons.

First order neuron:

- Carries signal from the periphery to the spinal cord.
- Located in the dorsal root ganglion.

Second order neuron:

- Carries signal from the spinal cord to the thalamus.
- Located in the spinal cord.
- Commonly decussate.

Third order neuron:

- Carries signal from the thalamus to the primary sensory cortex.
- Located in the thalamus.

Dermatome:

- Each spinal nerve innervates a segmental field of the skin called dermatome.

Pain:

- It is highly unpleasant physical sensation caused by illness or injury and causes individual to react to remove the pain stimulus.

Pain receptors:

- Pain receptors in the skin and other tissues are all free nerve endings.
- These receptors adapt very little and sometimes not at all. It is important b/c it allows pain to keep the person apprised of a tissue damaging stimulus as long as it persists.

Hyperalgesia:

- Increase in sensitivity of the pain receptors is called hyperalgesia.

Types of stimuli that excite pain receptors:

- There are three types of stimuli that elicit pain, mechanical, thermal and chemical pa stimuli.
- Chemicals that excite the chemical type of pain are bradykinin, serotonin, histamine an potassium ions.
- Prostaglandins and substance p enhance the sensitivity of pain endings.

Types of pain:

- There are two types of pain.

Fast pain:

- Felt within about 0.1 sec after a pain stimulus is applied.
- Also called sharp pain, pricking pain, acute pain and electric pain.
- Felt when a needle is stuck into the skin, skin is cut with a knife, skin is acutely burned an when the skin is subjected to electric shock.
- Not felt in most deep tissues of the body.
- Elicited by mechanical and thermal pain stimuli.
- It is transmitted to spinal cord by small type Aδ fibers at velocity of 6-30 m/sec.
- Localization is precise.

Slow pain:

- Begins only 1 sec or more after a pain stimulus is applied and then increases slowly.
- Also called slow burning pain, aching pain, throbbing pain, nauseous and chronic pain.
- Associated with tissue damage.
- Occur both in skin and any deep tissue.
- Elicited by mechanical, thermal and chemical pain stimuli.
- Transmitted to spinal cord by type C fibers at velocity of 0.5-2 m/sec.
- Localization is imprecise.

Pathways for transmission of pain signals into CNS:

- All pain receptors are free nerve endings. These endings use two separate pathways for transmitting pain signals into the CNS.

Neospinothalamic tract for fast pain:

- The fast type Aδ pain fibers transmit mainly mechanical and acute thermal pain.
- Glutamate is the neurotransmitter substance secreted in the spinal cord at the type Aδ pain nerve fiber endings.

Pathway:

- Fast pain fibers terminate mainly in lamina I (lamina marginalis) of the dorsal horns. There they excite second order neurons of the neospinothalamic tract.
- Second order neurons give rise to long fibers that cross immediately to the opposite side of the spinal cord through the anterior commissure and then turn upward, passing to the brain in the anterolateral columns.
- A few fibers terminate in the reticular areas of the brain stem but most pass all the way to the ventrobasal complex of the thalamus. The signals are then transmitted to other basal areas of the brain as well as to somatosensory cortex.

Paleospinothalamic pathway for slow pain:

- Much older system and transmits pain mainly from peripheral slow type C pain fibers, also it does transmit some signals from type Aδ fibers as well.
- The type C pain fiber terminals entering the spinal cord release both glutamate and substance P transmitter. Glutamate is the neurotransmitter involved in transmitting fast pain into the CNS and substance P is concerned with slow chronic pain.

Pathway:

- In this pathway the peripheral fibers terminate in the spinal cord in laminae II and III of the dorsal horns which together are called substantia gelatinosa.
- Most of the signals then pass through additional short fiber neurons within the dorsal horn before entering mainly lamina V. Here the last neurons in the series give rise to long axons that mostly join the fibers from the fast pain pathway, passing first through the anterior commissure to the opposite side of the cord, then upward to the brain in the anterolateral pathway.

Removal of the somatic sensory cortex:

- Complete removal of the somatic sensory areas of the cerebral cortex does not prevent pain perception.

Arousal system of the brain:

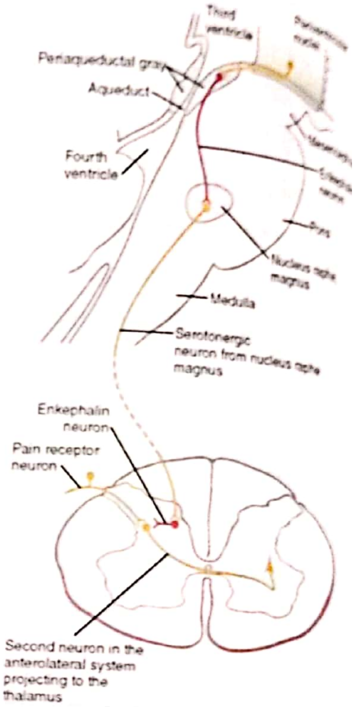
- Reticular area of the brainstem and intralaminar nuclei of the thalamus constitute part of the brain arousal system.

Surgical interruption of pain pathway:

- To provide pain relief, the pain nervous pathways can be cut at any one of several points.

- If the pain is in the lower part of the body, a cordotomy in the thoracic region of the spi cord often relieves the pain.
- To perform a cordotomy the spinal cord on the side opposite to the pain is partially cut its anterolateral quadrant to interrupt the anterolateral sensory pathway.

Analgesia system in the brain and spinal cord:



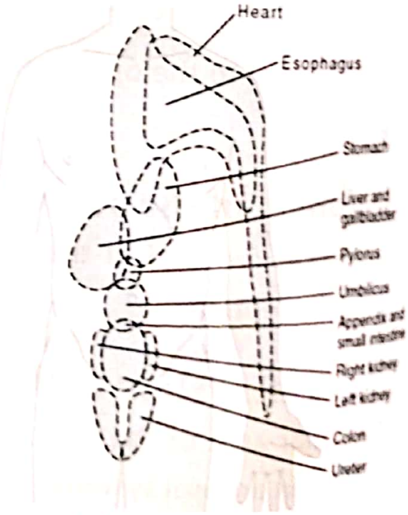
Analgesia system of the brain and spinal cord

- The degree to which a person reacts to pain varies.
- This variation partly results from a capability of the brain itself to suppress input of pain signals to the nervous system by activating a pain control system called an analgesia system.
- The analgesia system consist of three major components,
  - i) The periaqueductal gray and periventricular areas of mesencephalon and upper pons.
  - ii) The raphe magnus nucleus and the nucleus reticularis paragigantocellularis.
  - iii) A pain inhibitory complex located in the dorsal horns of the spinal cord.
- Transmitter substances involved in the analgesia system are encephalin and serotonin.

Inhibition of pain transmission by tactile signals:

- Stimulation of large type Aβ sensory fibers from peripheral tactile receptors can depress transmission of pain signals from the same area b/c of local lateral inhibition in spinal cord.
- e.g: Rubbing the skin near painful area.

Referred pain:



Surface areas of referred pain

- When a person feels pain in a part of the body that is fairly remote from the tissue causing the pain. This phenomenon is called referred pain.
- It is important b/c in many visceral ailments the only clinical sign is referred pain.

Mechanism of referred pain:

- The branches of visceral pain fibers synapse in the spinal cord on the same second order neurons that receive pain signals from the skin. When the visceral pain fibers are stimulated, pain signals from the viscera are conducted through some of the same neurons that conduct pain signals from the skin and the person has the feeling that the sensations originate in the skin.

- e.g: Heart pain is referred to the chest and shoulder.

Visceral pain:

- It is the pain originating from internal organs within the thoracic, abdominal or pelvic cavities.
- The viscera have sensory receptors for no other modalities of sensation besides pain.
- Highly localized types of damage to the viscera seldom cause severe pain. For instance a surgeon can cut the gut entirely in two in a patient who is awake without causing significant pain.
- Any stimulus that causes diffuse stimulation of pain nerve endings throughout viscera causes pain that can be severe. e.g: ischemia of visceral tissue.
- The parenchyma of liver and the alveoli of lungs are completely insensitive to pain.
- All visceral pain that originates in the thoracic and abdominal cavities is transmitted through small type C pain fibers and therefore can transmit only the chronic aching type of pain.

Parietal pain:

- It results from irritation of the fibers that innervate the parietal wall.
- Parietal sensations are conducted directly into local spinal nerves.
- These sensations are sharp and can be localized directly over the painful area.

Herpes Zoster:

- Also called shingles b/c of a skin eruption.
- Usually shows up on just one side of the body and does not cross the midline.
- Caused by the reactivation of varicella zoster virus in a patient who has previously had chickenpox.
- This virus infects a dorsal root ganglion which causes severe pain in the dermatomal segment sub served by the ganglion.

Treatment:

- Antiviral drugs such as acyclovir.
- Topical lidocaine.

Tic douloureux or Trigeminal neuralgia:

- A condition in which the patient experience sudden attacks of excruciating pain in the distribution of mandibular or maxillary division with the ophthalmic division usually escaping.
- Its cause is a mechanoreceptive stimulus (e.g: pressure) rather than a pain stimulus.

Brown-Sequard syndrome:

- Also called cord hemisection.
- If the spinal cord is transected on only one side, then brown sequard syndrome occurs.

- It results in lesion of corticospinal tract, dorsal columns and spinothalamic tract. The effects of such transection can be predicted from the knowledge of above tracts.
- All motor functions are blocked on side of transection in all segments below transection due to lesion of corticospinal tract.
- Sensations of pain, heat, and cold served by spinothalamic pathway are lost on contralateral side of the body in all dermatomes two to six segments below level of transection.
- Sensations transmitted in dorsal column such as kinesthetic, position, vibration, discrete localization and two point discrimination are lost on ipsilateral side of transect ion.
- Discrete light touch impaired on side of transection b/c principle pathway for light touch is dorsal column.
- Crude touch which is poorly localized still persist b/c of partial transmission in contralateral spinothalamic tract.

Headache:

- A type of pain referred to the surface of the head from deep head structures.
- Brain tissues are insensitive to pain.
- Damaging the tentorium or stretching the dura and blood vessels of meninges can cause headache.
- Pain above tentorium cause referred pain to front half of the head.
- Subtentorial pain cause occipital headache referred to the posterior part of the head.
- Headache of meningitis cause extreme headache referred over the entire head.
- Removing as little as 20 ml of fluid from spinal canal causes intense intracranial headache.

Migraine headache:

- A common form of headache, may be unilateral or bilateral, recurring at intervals and associated with prodromal sensations such as nausea and visual disturbances.
- The prodromal visual disturbances are due to sympathetic vasoconstriction of the cerebral arteries supplying the visual cortex.
- The headache is chiefly due to dilation and stretching of other cerebral arteries and branches of the external carotid artery.
- It occurs about twice as frequently in women as in men.

Treatment:

- β-blockers bring relief to some patients due to reduction in cerebral vasodilation.

Headache caused by eye disorders:

- A person having difficulty in focusing eyes clearly may cause excessive attempts to focus the eyes, can result in reflex spasm in various facial and extraocular muscles which cause headache.

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Thermal receptors:

- There are three types of thermal receptors,

Cold receptors:

- Free nerve endings and specialized receptors attached to type Aδ and type C nerve fibers.
- Respond to temperature from about 10°C to 38°C.
- Cold signals are transmitted at velocity of about 20 m/sec.

Warmth receptors:

- Free nerve endings attached to type C nerve fibers.
- Respond to temperature from about 30°C to 45°C.
- Warmth signals are transmitted at velocity of about 0.4 to 2 m/sec.

Thermosensitive pain receptors:

- stimulated by extreme degrees of heat and cold.
- Respond to temperature below 10°C and above 45°C.
- **Note:**
  We have more cold receptors than warmth receptors.
- Cold signals are transmitted about 10 times faster than warmth signals.

Adaptation of thermal receptors:

- Thermal receptors adapts moderately and to a great extent.

Mechanism of stimulation of thermal receptors:

- These receptor are stimulated by changes in their metabolic rates.
- Changes in metabolic rates result from altering the intracellular chemical reactions by temperature.
- Not from direct physical effects of heat or cold on the nerve endings.

Spatial summation of thermal sensations:

- Number of cold or warmth endings in any one surface area of the body is less.
- It is difficult to judge gradations of temperature when small skin areas are stimulated.
- When a large area is stimulated all at once, the thermal signals from the entire area summate.

Part-III

THE SPECIAL SENSES

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Refractive index:

- It is the ratio of velocity of light in vacuum to the velocity of light in a specified medium.
- e.g. Refractive index of air is 1.

Refraction of light rays:

- It is the bending of light as it passes from one transparent medium into another.
- When light rays pass through a perpendicular interface, rays enter the second medium without deviating from their path. Its velocity decreases and wavelength becomes shorter.
- If light rays pass through an angulated interface, the rays bend if refractive indices are different.

Refractive indices of refractive surfaces:

Refractive surface	Refractive index
Air	1
Cornea	1.38
Aqueous humor	1.33
Lens	1.40
Vitreous humor	1.34

Lens:

- A piece of glass or other transparent material with curved sides used for concentrating or dispersing light rays.

Spherical lenses:

- These are optical lenses with curved surfaces that cause light rays to converge or diverge.
- The point from which these rays converge or appear to diverge is called focal point.

Types of spherical lenses:

- There are two types of spherical lenses,

Convex lens:

- It converge light rays.

Concave lens:

- It diverge light rays.

Cylindrical lens:

- It is a lens which focuses light into a focal line instead of a focal point as a spherical lens would.
- Convex cylindrical lens bends light rays from the two sides of the lens but not from the top or bottom, that is bending occurs in one plane. Thus parallel light rays are bent to a focal line.
- Concave cylindrical lens diverge light rays in only one plane in the same manner that convex cylindrical lens converge in one plane.

Combination of cylindrical lenses:

- Two cylindrical lenses crossed at right angles to each other perform the same function as one spherical lens of the same refractive power.
- The vertical cylindrical lens converge the light rays that pass through the two sides of the lens while the horizontal lens converge the top and bottom rays. Thus all the light rays come to a single focal point.

Focal length:

- The distance beyond a convex lens at which parallel light rays converge to a common foca point is called focal length of the lens.
- It is a measure of how strongly a system converges or diverge light rays.
- It is the inverse of the system optical power.
- Positive focal length indicates convergence of light.
- Negative focal length indicates divergence of light.
- Focal length formula as,

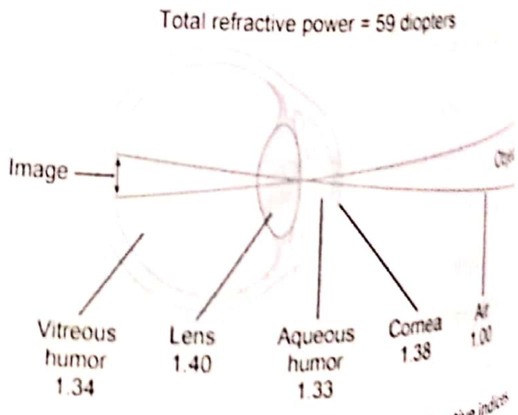
1/focal length = 1/distance of point source + 1/distance of focal point

Refractive power of a lens:

- Diopter is the unit of measurement of magnifying or refractive power of a lens.
- Diopter is equal to the reciprocal of the focal length measured in meters.
- Numerically diopter is equal to one meter divided by the focal length in meters.
- The more a lens bends light rays the greater is its refractive power.
- A spherical lens that converge parallel light rays to a focal point of 1 meter has a refractive power of +1 diopter.
- For cylindrical lenses in addition to its power the axis must be stated. If the focused line is horizontal its axis is zero degree, if focused line is vertical its axis is 90 degrees.

Reduced eye:

- Also called single refractive surface optical model eye.
- Represents the basic optical features of the real eye.
- Considering the eye as a single spherical refracting surface.
- Cornea is represented as the only source of refractive power of the eye.
- Anterior focal length - 17.2 mm.
- Posterior focal length - 22.6 mm.
- Total Dioptric power - 59 D, 2/3rd provided by the cornea and 1/3rd by lens.



The eye as a camera. The numbers are the refractive indic

Objective:

- Provide a basis for theoretical studies of the eye as an optical instrument.

Accommodation of eye:

- It is the mechanism by which the eye changes its refractive power by altering the shape of lens in order to focus objects at variable distances.

Mechanism of accommodation:

- Refractive power of the lens is 20 diopters about 1/3rd of the total refractive power.
- Importance of lens is that in response to nervous signal from brain its curvature can be increased to provide accommodation.
- The ciliary muscle is controlled by parasympathetic nerve signals transmitted through 3rd cranial nerve.
- Stimulation of parasympathetic nerves contracts both sets of ciliary muscle fibers which relaxes the lens ligaments thus allow the lens to become thicker and increase its refractive power.
- Now the eye will focus on near objects.

Formation of an image on the retina:

- An image formed on the retina is upside down with respect to the original object.
- The two lateral sides of the image are reversed.
- However the mind perceives objects in the upright position.

Presbyopia:

- It is the loss of accommodation of the lens that occurs with aging.
- Eyes can no longer accommodate for both near and far vision.
- Each eye remains focused permanently at a constant distance.

Correction:

- Wearing bifocal glasses with upper segment focused for far seeing and lower segment focused for near seeing.

Emmetropia:

- It means normal vision or zero refractive error.
- Images from distant objects are in sharp focus on the retina when the ciliary muscle is completely relaxed.

Hyperopia:

- Also known as farsightedness.
- Distant objects will be clear but near objects will be blurry.
- Cause is an eye ball that is too short or a lens that is too weak.
- Light rays focuses behind the retina.

Correction:

- Using convex lenses.

Myopia:

- Also known as nearsightedness.
- Near objects will be clear but distant objects will be blurry.
- Cause is an eyeball that is too long or a lens system that has too much focusing power.
- Light rays focuses in front of the retina.
- Myopic person has a far point for clear vision and cannot see anything that is further from far point.

Correction:

- Using concave lenses.

Astigmatism:

- It is an imperfection in the curvature of cornea or lens.
- Results from too great curvature of the cornea or lens in one plane of the eye.
- Light rays will be refracted to multiple areas of the retina.
- Accommodative power of the eye can never compensate for astigmatism.

Correction:

- Using cylindrical lenses.

Keratoconus:

- In this condition the normally dome shaped cornea becomes thin and odd shaped bulg cornea.
- Vision will be blurry and distorted.

Correction:

- Using contact lenses.

Cataracts:

- It is the clouding of the normally clear lens of the eye.
- Cataract begins when proteins in eye denatures and coagulate to form cloudy areas.
- It develops slowly and interferes with vision.
- Most common in older people.

Treatment:

- Surgical removal of the lens and after surgery an artificial lens is placed in place of the natural lens.

Optics of vision

Visual acuity:

- Refers to the clarity of vision.
- It is a measure of the ability of the eye to distinguish the details of objects.
- Normal visual acuity is 20/20.

Measurement:

- Visual acuity is usually measured using a snellen eye chart.
- Snellen eye chart consists of letters of different sizes placed at a distance of 20 feet.
- Snellen eye chart can measure how well you can see at a distance.
- 20/20 vision can see all the letters that a normal individual can see at 20 feet.
- 20/200 vision can see the letters at 20 feet that a normal individual can see at 200 feet.

Depth perception:

- It is the ability to determine the distance of an object from the eye.
- The distance can be determined by three main ways,
  - i) Sizes of images of known objects on the retina.
  - ii) Motion parallax
  - iii) Stereopsis

Stereopsis:

- It refers to the perception of depth and three dimentional structure obtained on the basis of visual information deriving from two eyes by individuals with normally developed binocular vision.

Ophthalmoscope:

- It is an instrument through which a doctor can look into a patient eye and see the retina clearly.

Aqueous humor:

- It is thin, transparent water like fluid similar to plasma.
- It lies in front of the lens in the anterior and posterior chambers of the eye.

Formation of aqueous humor:

- It is formed as an active secretion by the epithelium of the ciliary processes.
- Its secretion begins with active transport of sodium ions into the spaces b/w the epithelial cells.
- Rate of production is 2.5 µL/min or 3.6 mL/day.

Drainage of aqueous humor:

- After its production it enters the posterior chamber. It then flows into the anterior chamber through the pupil and is drained away through the spaces at the iridocorneal angle into the canal of schlemm, which is a venous sinus found near limbus. The small veins that lead

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from the canal of schlemm to the larger veins of the eye contain only aqueous humor and are called aqueous veins.

Functions of aqueous humor:

- It supports the wall of the eyeball by exerting internal pressure and thus maintains optical shape.
- It nourishes the cornea and lens b/c cornea and lens do not possess a blood supply.

Intraocular pressure:

- It is the pressure of fluid inside the eye.
- Normal intraocular pressure is 15 mmHg, with a range of 12-18 mmHg.
- It is measured clinically by using tanometer.

Glaucoma:

- It is a disease of the eye in which intraocular pressure becomes pathologically high.
- Results from increased resistance to fluid outflow through trabecular spaces into canal of schlemm.
- Most common cause of blindness b/c high IOP damage the optic nerve.

Treatment:

- β-blockers and carbonic anhydrase inhibitors decrease aqueous humor formation and reduce IOP.
- Prostaglandins and miotics facilitate drainage of aqueous humor and reduce IOP.

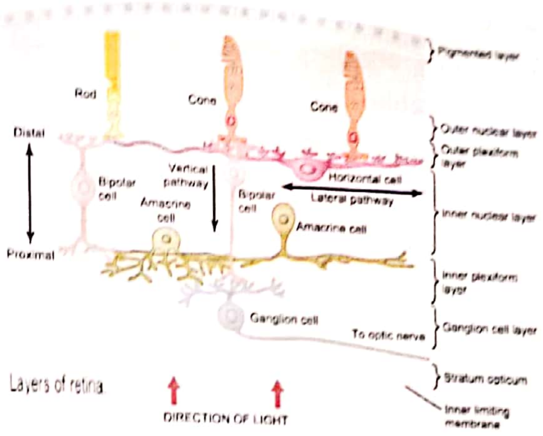
Retina:

- It is the light sensitive portion of the eye and send signal to the brain.
- It contains rods and cones.

Layers of retina:

The layers of retina from outside to inside are,

- Retinal Pigmented layer
- Layer of rods and cones projecting to the pigmented layer
- Outer nuclear layer containing cell bodies of rods and cones
- Outer plexiform layer
- Inner nuclear layer
- Inner plexiform layer
- Ganglionic cell layer
- Layer of optic nerve fibers
- Inner limiting membrane



Layers of the retina

Note:

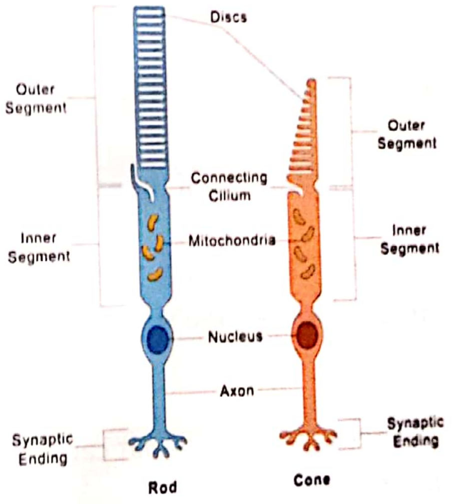
- Light enters the retina from inside of the eye, i.e it passes first through ganglionic layer and finally reaches the layer of rods and cones.

Fovea centralis of the retina:

- It is a depression in the center of the retina.
- About 0.3 mm in diameter.
- Composed entirely of cones.
- Specialized for maximum visual acuity.

Rods:

- Photoreceptors of rod shape
- More in number
- Found in the periphery of the retina
- Major segments are outer segment, inner segment, Nucleus, synaptic body
- Outer segment contain rhodopsin pigment made up of vitamin A
- Rods are more sensitive and less adaptable
- Provide vision during dim light or night
- Do not give color vision, responsible for black and white vision
- Lack of rhodopsin in the rods may cause night blindness



Functional parts of the rods and cones.

Cones:

- Photoreceptors of cone shape
- Less in number
- Found in the center of the retina
- Major segments are outer segment, inner segment, nucleus, synaptic body
- Outer segment contain iodopsin pigment
- Cones are less sensitive (about 30 to 300 times less sensitive than rods) and adaptable
- Chemical events of vision occur about four times as rapidly in cones as in rods
- Provide vision during day or bright light
- Provide color vision which is of three types: red, blue and green
- Lack of iodopsin in the cones may cause color blindness

Retinal pigmented layer:

- It contains black pigment melanin which prevents light reflection in the eyeball.
- In its absence light would be reflected in all directions in the eyeball and cause di lighting of the retina.
- It also stores large quantity of vitamin A.

Albinism:

- Congenital lack of melanin pigmentation.
- Due to defect an enzyme tyrosinase which is involved in the production of melanin.
- Having light skin and hair and are sensitive to light.

Blood supply of the retina:

- Nutrient blood supply for the internal layers of the retina is derived from the central reti artery.
- Outermost layers of the retina depend on diffusion from the choroid blood vessels.

Retinal detachment:

- In retinal detachment the neural retina detaches from the pigment epithelium.

Causes:

- Injury to the eyeball that cause fluid or blood to accumulate b/w neural retina and pigme epithelium.
- Contracture of fine collagenous fibrils in the vitreous humor which pull areas of the ret toward the interior of the globe.

Symptoms:

- Flashes of light
- Blurred vision

- Curtain like shadow over visual field

Treatment:

Treatment:

- Surgery

Rhodopsin:

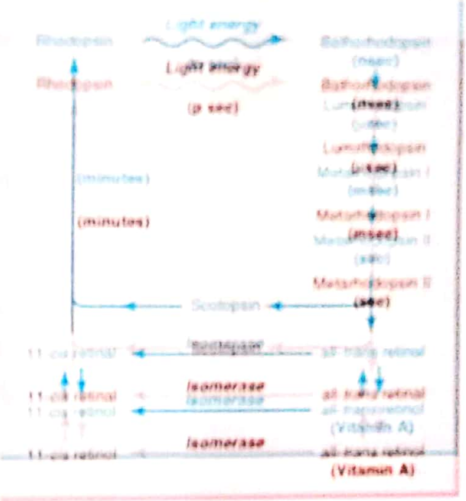
Rhodopsin:

- Light sensitive pigment
- Combination of the protein scotopsin and the carotenoid pigment 11- cis retinal.
- Present in the outer segment of the rod about 40%.

Decomposition of rhodopsin:

Decomposition of rhodopsin:

- Rhodopsin undergoes a cyclic decomposition and reconstitution in response to light.
- When light falls on rhodopsin, it begins to decompose. Cause of this decomposition is photo-activation of electrons in the retinal portion of rhodopsin.
- Cis-form of retinal changes into all-trans form.
- The reactive sites of all-trans retinal no longer fits with the reactive sites on protein scotopsin.
- All-trans retinal begins to pull away from the scotopsin. The immediate product is bathorhodopsin which is partially split combination of all-trans retinal and scotopsin.



The rhodopsin-retinal visual cycle in the rod

- Bathorhodopsin decays in nanoseconds to lumirhodopsin.
- The lumirhodopsin decays in microseconds to metarhodopsin I.
- The metarhodopsin I decays in milliseconds to metarhodopsin II and finally in seconds into scotopsin and all-trans retinal.
- Metarhodopsin II also called active form of rhodopsin excites chemical changes in the rods and the rods then transmit the visual image into CNS.

Reformation of rhodopsin:

Reformation of rhodopsin:

- First step is to convert all-trans retinal into 11-cis retinal. This requires energy aid is catalyzed by the enzyme retinal isomerase.
- The 11-cis retinal automatically recombines with scotopsin to reform rhodopsin.

Night blindness:

Night blindness:

- Also called nyctalopia.
- It is a condition characterized by an abnormal inability to see in dim light or at night.
- Caused by vitamin A deficiency.

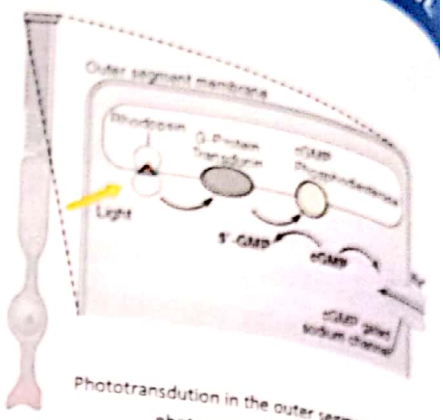
Treatment:

Treatment:

- Vitamin A supplements.

The rod receptor potential:

- The rod receptor potential is hyperpolarizing, not depolarizing.
- When rhodopsin decomposes, it decreases the rod membrane conductance for sodium ions in the outer segment of the rod. This causes hyperpolarization of the entire rod membrane.
- In the outer segment of the rod, the rod membrane in the dark state is leaky to sodium ions that flow through CGMP gated channels.
- During light the CGMP gated sodium channels are closed and reduces inward sodium current.
- When the rod is not excited electronegativity inside the membrane of the rod is -40 mv while at maximum light intensity the membrane potential is -70 mv.



Phototransdution in the outer segment of the photoreceptor membrane

Mechanism by which rhodopsin decomposition decreases sodium conductance:

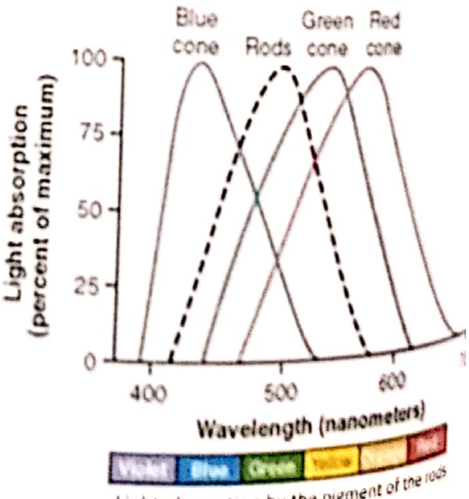
- When light is absorbed by the rhodopsin, the activated rhodopsin stimulates a G-protein called transducing present in the membrane of the discs and cell membrane of the rod, which then activates CGMP phosphodiesterase, an enzyme that catalyzes the breakdown of CGMP to 5'-CGMP.
- The reduction in CGMP closes the CGMP gated sodium channels and reduces the inward sodium current.
- Within about a second rhodopsin kinase an enzyme present in the rod inactivates the activated rhodopsin.

Duration of receptor potential of the rod:

- The receptor potential that occurs in the rods reaches a peak in about 0.3 sec and lasts for a sec.
- All chemical events of vision occur about four times as rapidly in cones as in rods.

Logarithmic relation of receptor potential to light intensity:

- The receptor potential is approximately proportional to the logarithmic of light intensity.



Light absorption by the pigment of the rods and by the pigments of cones

Photochemistry of color vision by the cones:

- The color sensitive pigment of the cones is iodopsin.
- It is combination of retinal and photopsin.
- There are three types of color pigments in cones blue, green and red sensitive pigments.
- Each cone has only one of the three types of color

pigments making the cones selectively sensitive to different colors blue, green or red.

- The absorption curves of blue, green and red pigments in cones show peak absorbencies at light wavelengths of 445, 535 and 570 nanometers respectively while for rod it is 505 nanometers.

Visual adaptation:

- It is the ability of the retina of the eye to adjust to various levels of light.

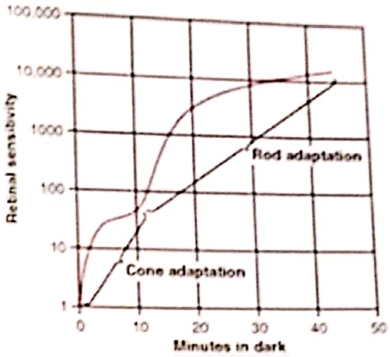
Types:

Light adaptation:

- If a person remains in bright light for long time concentration of photochemicals reduced and sensitivity of the eye to light is also reduced, this is called light adaptation.

Dark adaptation:

- If a person remains in dark light for long time concentration of photochemicals increases and sensitivity of the eye to light is also increased, this is called dark adaptation.



Dark Adaption of cone and rod

Interpretation of color by the nervous system:

- The human eye and brain together translate light into color.
- A monochromatic orange light with a wavelength of 580 nm stimulates the red cones to a stimulus value of about 99 (99% of the peak stimulation at optimum wavelength), the green cones to a value of 42 and the blue cones are not stimulated. This set of ratios- 99:42:0 is interpreted by the nervous system as orange.
- A monochromatic blue light with a wavelength of 450 nm gives a stimulated set of ratios- 0:0:97 for red, green and blue cones respectively which are interpreted by the nervous system as blue.
- A set of ratios - 83:83:0 are interpreted as yellow.
- A set of ratios – 31:67:36 are interpreted as green.
- About equal stimulation of all the red, green and blue cones gives one the sensation of white.

Red - Green color blindness:

- It is a genetic disorder that occurs exclusively in males.
- Genes in the female X chromosome code for the respective cones.
- Color blindness never occurs in female b/c at least one of the two X chromosomes always has a normal gene for each type of cone.
- Color blindness is passed from mother to son and the mother is color blindness carrier.
- About 8% of all women are color blindness carriers.

Protanope:

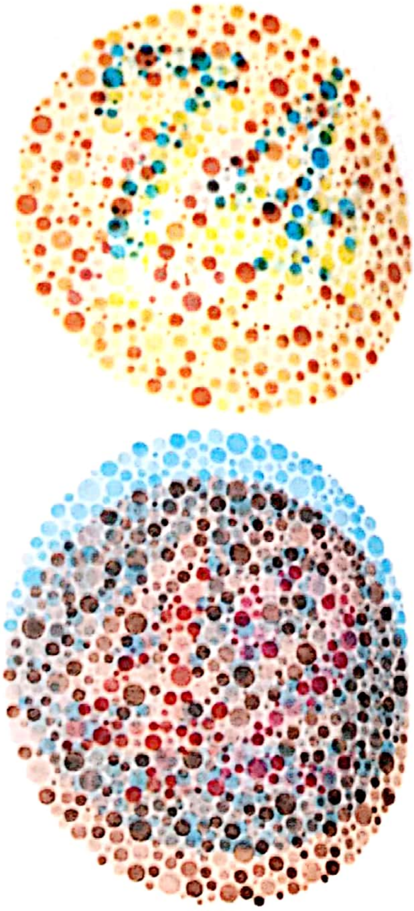
Protanope:

- A person with loss of red cones is called a protanope.
- This person has a shortened visual spectrum at the long wavelength end.

Deutranope:

Deutranope:

- A person with loss of green cones is called a deuteranope.
- This person has a normal visual spectral width.


Color Test charts

Color Test charts:

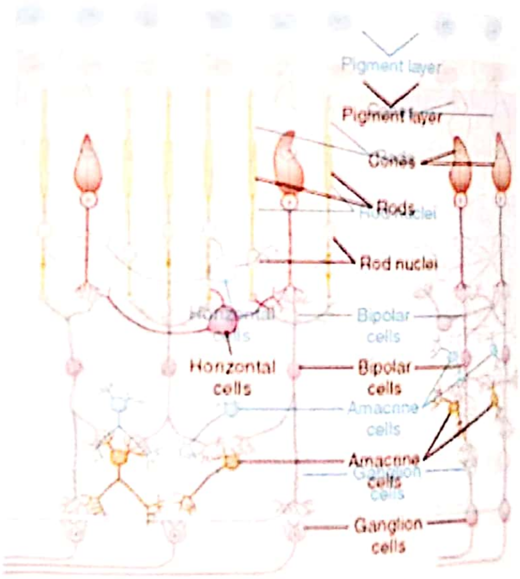
Color Test charts:

- A rapid method for determining color blindness is based on the use of spot charts.
- These charts are arranged with a confusion of spots of different colors.
- In one chart, a person with normal color vision reads "74" whereas a red-green color blind person reads "21".
- In another chart, a person with normal color vision reads "42" whereas a red color blind person reads "2" and a green color blind person reads "4".

Neural function of the retina:

Neural function of the retina:

- The different neuronal cell types are,



Neural organization of the retina

The photoreceptors - the rods and cones:

The photoreceptors - the rods and cones:

- Transmit signals to the outer plexiform layer where they synapse with bipolar cells and horizontal cells.

The horizontal cells:

The horizontal cells:

- Transmit signals horizontally in the outer plexiform layer from the rods and cones to bipolar cells.

The bipolar cells:

The bipolar cells:

- Transmit signals vertically from the rods and cones to ganglion cells and amacrine cells.

The amacrine cells:

The amacrine cells:

- Transmit signals in two directions, either directly from bipolar cells to ganglion cells or horizontally within the inner plexiform layer.

The ganglion cells:

The ganglion cells:

- Transmit output signals from the retina through the optic nerve into the brain.

The interplexiform cells:

- Transmit signals in the retrograde direction from the inner plexiform layer to the outer plexiform layer. These cells provide feedback from inner retina to outer retina.

Cone visual pathway:

- The optic nerve fibers that conduct cone visual signals are larger than those that conduct rod visual signals and the signals are conducted to the brain 2 to 5 times as rapidly.
- There are three neurons in direct cone visual pathway:
  - i) Cones
  - ii) Bipolar cells
  - iii) Ganglion cells
- Horizontal cells transmit inhibitory signals laterally in the outer plexiform layer.
- Amacrine cells transmit inhibitory signals laterally in the inner plexiform layer.

Rod visual pathway:

- There are four neurons in direct rod visual pathway:
  - i) Rods
  - ii) Bipolar cells
  - iii) Amacrine cells
  - iv) Ganglion cells
- Horizontal and amacrine cells provide lateral connectivity.

Neurotransmitter released by the retinal neurons:

- The rods and cones release glutamate.
- Different types of amacrine cells secrete different types of neurotransmitter. e.g: GABA and glycine, all of which normally function as inhibitory neuroyransmitters.
- The transmitters of bipolar, horizontal and interplexiform cells are unknown.

Transmission of signals in the retinal neurons:

- The only retinal neurons that transmit visual signals by means of action potentials are the ganglion cells.
- All other retinal neurons conduct their visual signals by electrotonic conduction.
- In the rods and cones even conduction from their outer segments to the synaptic bodies is by electrotonic conduction.

Lateral inhibition of visual signal:

- It enhances visual contrast.
- It is the function of horizontal and amacrine cells.

Ganglion cells and optic nerve fibers:

- Each retina contains about 100 million neurons and 3 million cones.
- The number of ganglion cells is only about 1.6 million.

- About 60 rods and 2 cones converge on each ganglion cell.
- Ganglion cells transmit signals by means of action potentials.
- The optic nerve fiber leading from the ganglion cell to the brain. So optic nerve fibers of ganglion cells.

Parvocellular ang Magnocellular cells:

- These are two general classes of retinal ganglion cells

Parvocellular cells (P cells):

- Also known as beta cells or in the central retina as midget ganglion cells.
- Project to the parvocellular layer of lateral geniculate nucleus of the thalamus.
- Receptive fields are much smaller.
- Its axons conduct impulses slowly.
- Its responses to stimuli can be sustained.
- Sensitive to color stimuli.

Magnocellular cells (M cells):

- Also known as alpha cells or parasol cells.
- Project to the magnocellular layer of lateral geniculate nucleus of the thalamus.
- Receptive fields are larger.
- Its axons conduct impulses rapidly.
- Its responses are more transient.
- Not sensitive to color stimuli.
- More sensitive to black and white stimuli.

Melanopsin:

- A type of photopigment present in sub retinal ganglion cells.
- Plays an important role in circadian rhythms.

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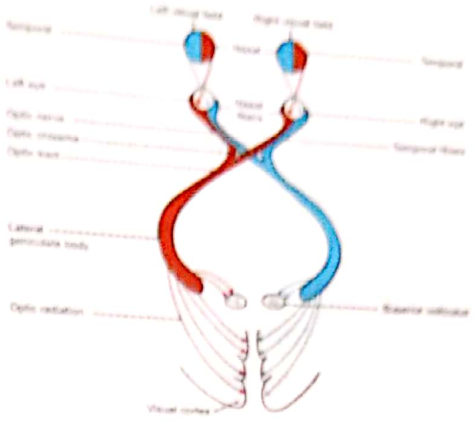
Visual pathway:

- The visual nerve signals leave the retinas through the optic nerves.
- At the optic chiasm, the optic nerve fibers from the nasal halves of the retinas cross to the opposite sides, where they join the fibers from opposite temporal retinas to form the optic tracts.
- The fibers of each optic tract synapse in the dorsal lateral geniculate nucleus of the thalamus and form there, geniculocalcarine fibers pass by way of optic radiation to the primary visual cortex in the calcarine fissure area of the medial occipital lobe.



Visual pathway

- Visual fibers also pass to other several areas of the brain,
- From optic tracts to suprachiasmatic nucleus of hypothalamus to control circadian rhythms.
- Into the pretectal nuclei in the midbrain to activate pupillary light reflex.
- Into the superior colliculus, to control rapid directional movements of the two eyes.
- Into the ventral lateral geniculate nucleus of the thalamus to control some behavioral functions of the body.

Dorsal lateral geniculate nucleus:

- It relays visual information from optic tract to the visual cortex by way of the optic radiation.
- The signals from the two eyes are kept apart in dorsal lateral geniculate nucleus.
- This nucleus is composed of six nuclear layers.
- Layers ii, iii and v receive signals from the lateral half of the ipsilateral retina.
- Layers i, iv and vi receive signals from the medial half of the contralateral retina.
- It also gate transmission of signals to the visual cortex. The nucleus receives gating control signals from corticofugal fibers and reticular areas of the mesencephalon. Both of these sources are inhibitory.
- The dorsal lateral geniculate nucleus is divided in another way as,

Magnocellular layer:

- Layers i and ii are called magnocellular layers b/c they contain large neurons.
- These neurons receive input from M retinal ganglion cells.
- This system provides a rapidly conducting pathway to visual cortex.
- This system is color blind and its point to point transmission is poor.

Parvocellular layers:

- Layers iii and vi are called parvocellular layers b/c they contain small to median sized neurons.
- These neurons receive input from p retinal ganglion cells that transmit color.
- This system convey accurate point to point spatial information but at moderate velocity of conduction.

Visual cortex:

- It is located on the medial aspect of the occipital lobes.
- It is divided into primary visual cortex and secondary visual cortex.

Primary visual cortex:

- Also called visual area I or the striate cortex.
- Located in the calcarine fissure area.
- Brodmann,s area 17 is primary visual cortex.
- It is the terminus of direct visual signals from the eyes. Signals from the macular area of retina terminate near the occipital pole, whereas signals from the more peripheral retin terminate in concentric half circles anterior to the pole.
- It has six distinct layers.
- Removal of the primary visual cortex in human causes blindness.

Secondary visual cortex:

- Also called visual association area or visual area ii.
- It lies lateral, anterior, superior and inferior to the primary visual cortex.
- Brodmann,s area 18 is secondary visual area.

Vertical Neuronal columns in the visual cortex:

- The visual cortex is organized structurally into vertical columns of neuronal cells.
- Each column have a diameter of 30 to 50 μm.

Field of vision:

- It is the visual area seen by an eye fixed straight at a point.

Perimetry:

- It is the systemic measurement of visual field function.
- In all perimetry charts, a blind spot caused by lack of rods and cones in the retina over t optic disc is found about 15 degrees lateral to the central point of vision.

Scotomata:

- Blind spots found in portions of the retina other than the optic disc area are ca scotomata.
- It is frequently caused by damage to the optic nerve resulting from glaucoma.

Retinitis pigmentosa:

- In this disease potions of the retina degenerate and excessive melanin pigment is deposit in the degenerate areas
- It usually causes blindness in the peripheral field of vision first and then gradual encroaches on the central areas.
- It is diagnosed by perimetry.

Effects of lesions in the optic pathway on the fields of vision:

Lesion of optic nerve:

- Lesion of the optic nerve causes blindness of the affected eye.

Note:

- Normally, the nasal half of retina looks at the temporal half of field of vision while the temporal half of retina looks at the nasal half of the visual field.

Lesion of optic chiasm:

- Its lesion causes bi-temporal hemianopia.
- In this condition the nasal half of each retina is blinded, which means that the person is blind in the temporal field of vision for each eye.
- It frequently results from tumors of the pituitary gland.

Lesion of optic tract:

- Its lesion causes homonymous hemianopia.
- If the right optic tract is divided, a left temporal hemianopia and a right nasal hemianopia will occur.

Fixation movement of the eyes:

- Fixation movements are controlled by two neuronal mechanisms,

Voluntary fixation mechanism:

- It allows a person to move the eyes voluntarily to find the object on which he or she wants to fix the vision.
- Controlled by a cortical field located bilaterally in the premotor cortical regions of the frontal lobes.
- Bilateral destruction of these areas makes it difficult for a person to unlock the eyes from one point of fixation and moves them to another point. It is necessary to blink the eyes or put a hand over the eyes for a short time, which allows the eyes to be moved.

Involuntary fixation mechanism:

- It holds the eyes firmly on the object once it has been found.
- It results from a negative feedback mechanism that prevents the object of attention from leaving the foveal portion of the retina.
- It is controlled by secondary visual areas in the occipital cortex, located mainly anterior to the primary visual cortex.
- Bilateral destruction makes it difficult to keep eyes directed toward a given fixation point.

Saccadic movement of the eyes:

- Saccades are rapid, ballistic movements of the eyes that abruptly change the point of fixation.

- When a visual scene is moving continually before the eyes, such as when a person is riding in a car, the eyes fix on one highlight after another in the visual field, jumping from one to the next at a rate of two to three jumps per sec, these jumps are called saccades.
- The saccades occur so rapidly that no more than 10% of the total time is spent moving the eyes, with 90% of the time being allocated to the fixation sites.
- The brain suppresses the visual image during saccades so the person is not conscious of the movements from one point to another.

Persuit movement:

- Persuits are smooth eye movements in which the eyes remain fixed on a moving object.

Strabismus:

- Also called squint or cross eye.
- It is a condition in which the eyes do not properly align with each other when looking at an object
- Its basic types are horizontal strabismus, torsional strabismus and vertical strabismus.

Causes:

- It can be caused by problems with eye muscles, the nerves that supply eye muscles or the control center in the brain that directs eye movements.

Treatment:

- It can be treated with eye glasses, prisms, vision therapy or eye muscle surgery

Autonomic innervation of the eyes:

- The eye is innervated by both parasympathetic and sympathetic nerve fibers.

Parasympathetic supply:

- Its preganglionic fibers arise in the Edingerwestphal nucleus and then pass to ciliary ganglion which excites,

i) The ciliary muscle that controls focusing of the eye lens.
ii) The sphincter of the iris that constricts the pupil.

Sympathetic supply:

- It originates in the intermediolateral horn cells of the first thoracic segment of the spinal cord.
- Its fibers innervate the radial fibers of the iris (which dilate the pupil) and extraocular muscles of the eye.

Control of accommodation or focusing the eyes:

- Accommodation results from contraction or relaxation of the eye ciliary muscle.
- Contraction of the ciliary muscle causes increased refractive power of the lens and relaxation causes decreased refractive power.

- Accommodation of the lens is regulated by a negative feedback mechanism that automatically adjusts the refractive power of the lens to achieve the highest degree of visual acuity.

Control of pupillary diameter:

Miosis:

- Stimulation of the parasympathetic nerves excites the pupillary sphincter muscle, thereby decreasing the pupillary aperture which is called miosis.

Mydriasis:

- Stimulation of the sympathetic nerves excites the radial fibers of the iris and causes pupillary dilation which is called mydriasis.

Pupillary light reflex:

- When light is shone into the eyes the pupils constrict a reaction called the pupillary light reflex.
- When light falls on the retina impulses pass from the optic nerves to the pretectal nuclei. Then impulses pass to the Edinger-westphal nucleus and finally back through parasympathetic nerves to constrict the sphincter of the iris.
- Conversely in darkness the reflex becomes inhibited which results in dilation of the pupil.
- The function of the light reflex is to help the eye adapt rapidly to changing light conditions.

Argyll Robertson pupil:

- It is a pupil that fails to respond to light but does respond to accommodation and is also very small.
- It is caused by lesion interapting fibers that run from pretectal nucleus to Edinger-westphal nucleus on both sides.

Adie tonic pupil:

- It is a pupil that has decreased or absent light reflex and weak accommodation reflex.
- It is caused by disorder of parasympathetic innervation of constrictor pupillae muscle or damage to ciliary ganglion.

Horner's syndrome:

- It is caused by an interruption of the sympathetic nerve supply to the head.

Symptoms:

- It includes,
- Constriction of the pupil (miosis).
- Drooping of the upper eyelid (ptosis).
- Lack of sweating plus vasodilation (anhydrosis).
- Depression of the eyeball into the orbital cavity (Exophthalmos).

Ossicular system:

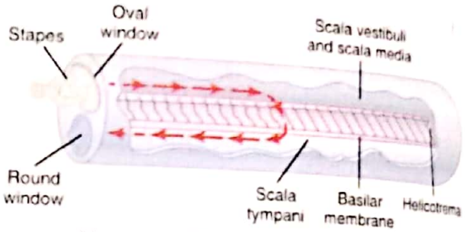
- The ossicular lever system in ear increases the force of movement about 1.3 times.
- The surface area of tympanic membrane is about 55 mm^2 whereas the surface area of stapes is 3.3 mm^2.
- This causes about 22 times as much total force to be exerted on the fluid of cochlea as exerted by the sound waves against the tympanic membrane.

Attenuation reflex:

- When loud sounds are transmitted through the ossicular system, a reflex occurs after a latent period of 40 to 80 milli sec to cause contraction of the stapedius and tensor tympani muscles which is called attenuation reflex.
- The tensor tympani muscle pulls the handle of malleus inward while the stapedius muscle pulls the stapes outward.
- Its role is to protect the cochlea from damaging of loud sound and to mask low frequency sounds in loud environment which allow a person to concentrate on sounds of frequency above 1000 cycles/sec.

Hyperacusis:

- It is excessive hearing sensitivity due to paralysis of stapedius muscle.
- Cause is facial nerve lesion.



Movement of fluid in the cochlea after forward thrust of the stapes

Hypoacusis:

- It is low hearing sensitivity due to paralysis of tensor tympani muscle.
- Cause is trigeminal nerve lesion.

Cochlea:

- It is embedded in a bony cavity in the temporal bone called bony labyrinth.
- It is a system of coiled tubes consist of three tubes coiled side by side,
- i) the scala vestibuli ii) the scala media iii) the scala tympani
- The scala vestibule and scala media are separated from each other by Reissner's membrane, also called vestibular membrane.
- The scala tympani and scala media are separated from each other by the basilar membrane.
- The scala vestibule and scala tympani contain perilymph which has high sodium concentration.
- The scala media contains endolymph which has high potassium concentration.
- The scala vestibuli and scala tympani communicate directly with subarachnoid space, so the perilymph is almost identical to CSF.
- The endolymph is different fluid secreted by the stria vascularis.
- The scala vestibule and scala tympani communicate with each other at helicotrema.

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Organ of corti:

On the surface of basilar membrane lies the organ of corti (the receptor organ).

- It contains electromechanically sensitive cells, the inner and outer hair cells.
- Hair cells are the receptive end organs that generate nerve impulses in response to sound vibrations.
- Inner hair cells are arranged in single row numbering about 3500 and 12 µm in diameter.
- Outer hair cells are arranged in three or four rows numbering about 12,000 and 8 µm in diameter.

Excitation of the hair cells:

- Hair cells are the receptive end organs that generate nerve impulses in response to sound vibration.
- Sterocilia or minute hairs project upward from the hair cells and are embedded in the surface gel coating of the tectorial membrane, which lies above the sterocilia in the scala media.
- Bending of sterocilia toward the kinocilium (tallest sterocilia) causes depolarization of hair cells.
- Bending of sterocilia away from the kinocilium causes hyperpolarization of hair cells.
- The neurotransmitter released by hair cells is glutamate.

Endocochlear potential:

- An electrical potential of about +80 mv exists all the time b/w endolymph and perilymph, with positivity inside the scala media and negativity outside, which is called endocochlear potential.
- It is generated by continual secretion of positive potassium ions into the scala media by stria vascularis.
- The importance of endocochlear potential is that the top of the hair cells are bathed by endolymph of the scala media whereas the perilymph bathes the lower bodies of hair cells. The hair cells have a negative intracellulae potential of -70 mv with respect to perilymph but -150 mv with respect to endolymph at their upper surfaces that are bathed by endolymph.

Basilar membrane and sound frequency:

- It contains basilar fibers that project from the bony center of cochlea, the modiolus, toward the outer wall.
- The lengths of basilar fibers increase progressively from oval window to the helicotrema.
- The diameter of basilar fibers decreases from the oval window toward helicotrema, so their overall stiffness decrease.

- As a result the stiff short fibers near the oval window of the cochlea vibereate best at a very high frequency, whereas the lon limber fibers near helicotrema vibreate best at a low frequency.

Place principle:

- The principle method by which sound frequencies are discriminated from one another is based on the position along the basilar membrane that are more stimulated which is called the place principle.
- Place principle cannot discriminate sound frequencies below 200 cycles/sec.

Volley or frequency principle:

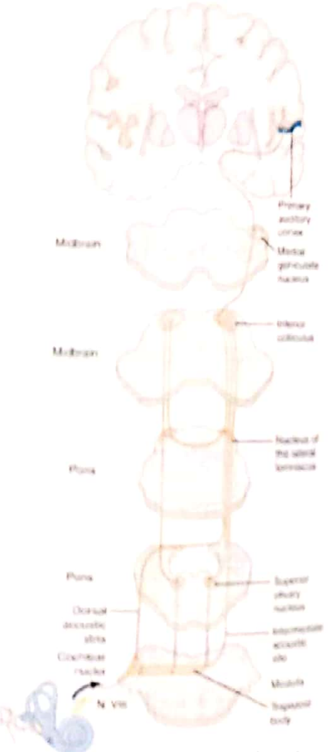
- This principle states that a group of neurons of auditory system respond to a sound by firing action potential slightly out of phase with one another so that when combined a greater frequency of sound can be encoded and sent to the brain to be analyzed.
- Low sound frequencies in the range of 20 to 200 cycles/sec can be discriminated by volley principle.

Frequency range of hearing:

- The frequency of sound that a pesson can hear is b/w 20 and 20 thousand cycles/sec.
- In old age this frequency range is usually shorten to 50 to 8 thousand cycle/sec or less.

Auditory nervous pathway:

- Nerve fibers from spiral ganglion of corti enter the cochlear nuclei located in medulla.
- At this point fibers synapse and second order neurons pass mainly to opposite side of brain and terminate in superior olivary nucleus, a few fibers also passes to superior olivary nucleus on the same side.
- From superior olivary nucleus the auditory pathway passes through lateral lemniscus and travel onto the inferior colliculus and then passes to the medial geniculate nucleus.
- Finally the pathway proceeds by way of the auditory radiation to the auditory cortex located in superior gyrus of temporal bone.
- Signals from both ears are transmitted through the pathways of both sides of the brain with a free ponderance of transmission in the contralateral pathway.



Auditory nervous pathways

Determination of the direction from which sound comes:

- A person determines the horizontal direction from which sound comes by two means,

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i) The time lag b/w the entry into one ear and its entry into the opposite ear.

ii) The difference b/w the intensities of the sound in the two ears.

Superioir olivary nucleus:

- The lateral superior olivary nucleus is concerned with detecting the direction from which sound is coming by simply comparing the difference in intensities of the sound reaching the two ears.
- The medial superior olivary nucleus has a specific mechanism for detecting the time lag b/w acoustical signal entering the two ears.

Conductive deafness:

- It is cause by impairment of the physical structures of the ear that conducts sound at self to the cochlea. i.e: outer ear, eardrum or middle ear ossicles.

Sensorineural deafness;

- It occurs from damage to the cochlea, auditory nerve or the brain.

Audiometer:

- It is amachine used to determine the nature of hearing disabilities.

Otosclerosis:

- It is abnormal bone formation causing fixation of the foot plate of the stapes into the oval window.
- The resulting limited movements of the stapes cause conductive deafness.

Otitis media:

- It is an acute infection of the middle ear.

Otorrhea:

- It is drainage of fluid from the external part of the ear canal.

Types of taste receptors:

- There are five types of taste receptors which can detect sour, salty, sweet, bitter and umami sensations.
- The sour taste is caused acid that is by the hydrogen ion concentration.
- The salty taste is caused by ionized salts, mainly by the sodium ion concentration.
- The sweet taste is caused by organic chemicals like sugar, glycols, alcohols, aldehydes and A.A.
- The bitter taste is caused by nitrogen containing long chain organic substances and alkaloids.
- Umami is the dominant taste of food containing L-glutamate such as meat extracts.

Threshold for taste:

- Threshold for stimulation of the sour taste by HCl is 0.0009M.
- Threshold for stimulation of salty taste by sodium chloride is 0.01M.
- Threshold for stimulation of sweet taste by sucrose is 0.01M.
- Threshold for stimulation of bitter taste by quinine is 0.000008M.
- Bitter taste sense is more sensitive than all the other senses b/c this sensation provides an important protective function against many dangerous toxins in food.

Taste blindness:

- Some people are taste blind for certain substances.
- A substance used frequently for demonstrating taste blindness is phenylthiocarbamide, for which about 15 to 30% of all people exhibit taste blindness.

The taste bud and its function:

- It has a diameter of about 1/30 mm and a length of about 1/16 mm.
- Adults have 3000 to 10,000 taste buds and children have a few more.
- It is composed of about 50 modified epithelial cells, some of which are supporting cells called sustentacular cells and other are taste cells.
- Taste cells are continually replaced by mitotic division of surrounding epithelial cells.
- Life span of each taste cell is about 10 days in lower animals but is unknown for humans.
- Outer tips of taste cells are arranged around a minute taste pore. From the tip of each taste cell several microvilli or taste hairs protrude outward into the taste pore. These microvilli provide receptor surface for taste.

Location of the taste buds:

- Taste buds are found on three types of papillae,
- i)Circumvallate papillae ii)Fungiform papillae iii)Foliate papillae
- Filiform papillae are taste blind b/c they do not have taste buds and are located on the anterior two-thirds of tongue.
- Circumvallate papillae form a V line on the surface of posterior tongue.
- Fungiform papillae are located on the flat anterior surface of tongue.
- Foliate papillae are located along the lateral surface of tongue.

The taste and the smell senses

Mechanism of taste buds stimulation:

- Membrane of the taste cell is negatively charged on the inside with respect to the outside.
- Application of a taste substance to the taste hairs causes partial loss of this negative potential and the taste cell becomes depolarized.
- For salty and sour taste sensations the receptor proteins open specific ion channels in the apical membrane of the taste cells, thereby activating the receptors.
- For sweet and bitter taste sensations, the receptor proteins activate second messenger transmitter substances CAMP inside the taste cells which elicit the taste signals.

Transmission of signals into the CNS:

- Taste impulses from the anterior two-thirds of the tongue pass first into the lingual nerve, then through the chorda tympani into the facial nerve and finally into the tractus solitarius in the brain stem.
- Taste impulses from circumvallate papillae on the back of tongue and from posterior regions of mouth and throat are transmitted through glossopharyngeal nerve into the tractus solitarius.
- A few taste signals from base of tongue and other parts of pharyngeal region are transmitted through vagus nerve into the tractus solitarius.
- All taste fibers synapse in the nuclei of tractus solitarius, which send second order neurons to ventral posterior medial nucleus of thalamus. From thalamus third order neurons are transmitted to the postcentral gyrus where it curls deep into the sylvian fissure and into opercular insular area.

Taste reflexes:

- From the tractus solitarius many taste signals are transmitted directly into the superior and inferior salivatory nuclei. These nuclei transmit signals to the salivary glands to control secretion of saliva during ingestion and digestion of food. So taste reflexes are integrated in the brain stem.

Adaptation of taste sensation:

- Taste sensations adapt rapidly.
- Adaptation of taste buds usually accounts for no more than half of this rapid adaptation.
- The final extreme degree of adaptation in the sensation of taste almost occurs in the CNS.

Sense of smell:

- The sense of smell is poorly developed in humans as compared with lower animals.
- In each nostril, the olfactory membrane has a surface area of 2.4 sq cm.

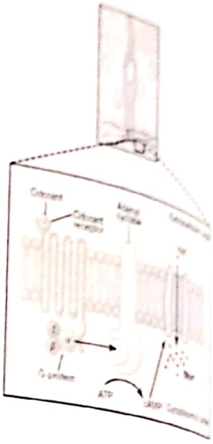
Olfactory cells:

- These are the receptor cells for smell sensation.
- These are bipolar nerve cells derived from the CNS.

- The mucosal end of olfactory cell forms a knob from which 4 to 25 olfactory cilia projec into the mucus.
- Olfactory cilia are 0.3 μm in diameter and 200 μm in length.
- These cilia react to odors in the air and stimulate the olfactory cells.
- Among olfactory cells are small Bowman glands that secrete mucus.

Mechanism of excitation of olfactory cells:

- The odorant receptor is seven pass receptor.
- The odor stimuli use CAMP second messenger system for excitation of olfactory cells.
- This CAMP opens sodium ion channel which allows large number of sodium to enter cell cytoplasm which increase the electrical potential in the positive direction, thus exciting the olfactory neuron and transmitting action potential into CNS by way of olfactory nerve.


Olfactory signal transduction

Membrane potential and action potential in olfactory cell:

- The membrane potential inside un-stimulated olfactory cells is about -55 mv.
- Most odorants cause depolarization of olfactory cell membrane, decreasing the negative potential from normal -55 to -30 mv, changing the voltage in the positive direction.

Olfactory adaptation:

- The olfactory receptors adapt about 50% in the first second after stimulation. Thereafter they adapt very slowly.
- Smell sensations adapt almost to disappearance within a minute. Most of the adaptation occurs within the CNS.

Transmission of smell signals into CNS:

- The olfactory nerve fibers leading from the olfactory bulb are called olfactory tract.
- Both the olfactory bulb and tract are anterior outgrowths of brain tissue.
- The olfactory tract enters the brain at the anterior junction b/w the mesencephalon and cerebrum, there the tract divides into two pathways, one passing medially into the medial olfactory area of the brain stem and the other passing laterally into the lateral olfactory area.

Medial olfactory area:

- It represents a very primitive olfactory system, consists of septal nuclei.

Lateral olfactory area:

- It represents a newer olfactory system, composed mainly of prepyriform and pyriform cortex and cortical portion of the amygdaloid nuclei.

Note:

- All sensory pathways except olfactory pathway synapse in the thalamus.

Anosmia:

- It is the loss of ability to detect smell.

Hyposmia:

- It is decreased sensitivity to smell.

Epistaxis:

- It is bleeding from the nose.
- Causes include nose picking and degeneration of the nasal septum resulting from chronic use of cocaine.
- Bleeding occurs from septal branches of sphenopalatine and facial vessels.

Part-IV

MOTOR PHYSIOLOGY

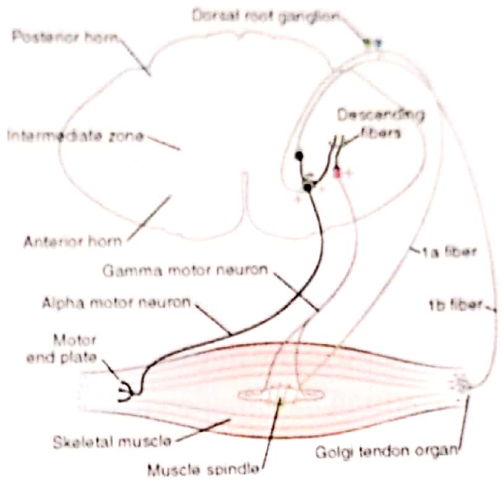
Motor Functions OF the Spinal Cord CH# 01

Anterior motor neurons:

- Give rise to nerve fibers that leave the cord by way of the anterior roots and innervate the skeletal muscle fibers.

Types of anterior motor neurons:

- There are two types, Alpha and Gamma,



Peripheral sensory fibers and anterior motor neurons innervating skeletal muscle.

Alpha motor neurons:

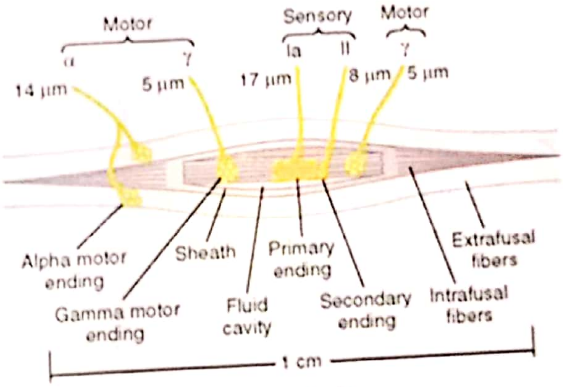
- Give rise to large type A alpha (Aα) motor nerve fibers.
- 14 µm in diameter.
- Innervate skeletal muscle fibers (Extrafusal muscle fibers).

Gamma motor neurons:

- Give rise to small type A gamma motor nerve fibers.
- 5 µm in diameter.
- Innervate intrafusal fibers (Muscle spindle).

Interneurons:

- Present in all areas of the cord gray matter and brain.
- Small, highly excitable and capable of firing as rapidly as 1500 times/sec.
- The corticospinal tract terminates on spinal interneurons.
- Connect spinal motor and sensory neurons and play vital roles in reflexes.



Muscle spindle

Renshaw cells:

- Located in the anterior horns of the spinal cord.
- Inhibitory cells transmit inhibitory signals to the surrounding motor neurons.
- Sharpen the signal.

Propriospinal tracts:

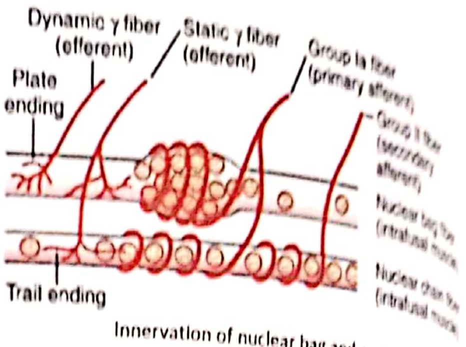
- Collection of ascending, descending, crossed and uncrossed nerve fibers that interconnect various levels of the spinal cord.
- Located in the white columns of the spinal cord where the columns meet the spinal central gray.
- Provide pathways for the multi-segmental reflexes.

Muscle sensory receptors:

- There are two types of muscle sensory receptors,

Muscle spindles:

- Distributed throughout the belly of the muscle.
- Send information to the nervous system about muscle length or rate of change of length.
- Each muscle spindle is 3 to 10 mm long.
- It is built around 3 to 12 tiny intrafusal muscle fibers.



Innervation of nuclear bag and nuclear chain muscle spindle fibers

Golgi tendon organs:

- Located in the muscle tendons.
- Transmit information about tendon tension or rate of change of tension.

Sensory innervation of the muscle spindle:

- The receptor portion of the muscle spindle is its central portion.
- In this central portion, the intrafusal muscle fibers do not have myosin and actin contracti elements.
- Two types of sensory endings are found in this central receptor area of the muscle spindle.

Primary Endings:

- Primary afferent endings or annulospiral endings are type I_a fibers.
- 17 µm in diameter.
- Transmits sensory signals to the spinal cord at a velocity of 70 to 120 m/sec.

Secondary Endings:

- They are type II fibers.
- 8 µm in diameter.
- Innervate the receptor region on one or both sides of the primary endings.

Types of muscle fibers:

- There are two types,

Extrafusal muscle fibers:

- They make up the bulk of the muscle.
- Provide force for muscle contraction.
- Innervated by Alpha motor neurons.

Intrafusal muscle fibers:

- They are embedded within the extrafusal fibers.
- Innervated by gamma motor neurons.

- Contain proprioceptive sensory receptors and constitute muscle spindle.

Types of intrafusal muscle fibers in muscle spindles:

- There are two types of muscle spindle intrafusal fibers,

Nuclear bag fibers:

- These fibers lie in the center of a muscle spindle.
- One to three in each muscle spindle.
- Nuclei are congregated or concentrated in bags.
- They cause excitation of the primary nerve ending.
- Detect the rate of change in muscle length.
- They are innervated by type I_a fibers (group I_a afferents).

Nuclear chain fibers:

- These fibers along with nuclear bag fibers make up the muscle spindle.
- Three to nine in each bundle.
- Of nuclei are aligned in a chain.
- Half the size of nuclear bag fibers.
- Cause excitation of secondary nerve endings and also of primary nerve ending.
- Detect static change in muscle length.
- They are innervated by group II afferents.

Response of primary and secondary endings to the length of the receptor:

Static response:

- When the receptor portion of the muscle spindle is stretched slowly, the number of impulses transmitted from both primary and secondary endings increases directly in proportion to the degree of stretching and the endings continue to transmit these impulses for several minutes which is called static response.
- The static response lasts as long as the muscle is being stretched.

Dynamic response:

- When the length of the spindle receptor increases suddenly, the primary endings are stimulated powerfully which is called dynamic response.
- The dynamic response lasts for only a moment in response to the initial sudden increase in muscle length.

Control of static and dynamic responses by Gamma motor nerves:

- Gamma dynamic motor nerves excites the nuclear bag fibers, the dynamic response is enhanced.
- Gamma static motor nerves excites the nuclear chain fibers, enhances the static response while having little influence on the dynamic response.

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Brain areas for control of the Gamma motor system:

- 31% of all motor fibers to muscles are small type A gamma efferent fibers.
- The gamma efferent system is excited by signals from the bulboreticular facilitatory region of brainstem and secondarily by impulses transmitted into the bulboreticular region from cerebellum, basal ganglia and cerebral cortex.

Reflex Action:

- It is the sudden involuntary response of the body to a stimulus.

Reflex arc:

- The anatomical pathway involved in reflex action is called reflex arc.

Components of reflex arc:

- Components of reflex arc are,
- Receptor
- Sensory nerve
- CNS
- Motor nerve
- Effector

Classification of reflexes on the basis of synapses:

Monosynaptic reflexes:

- These reflexes involve a single synapse in the receptor arc.
- Example is stretch reflex.

Bi-synaptic reflexes:

- These reflexes involve two synapses in the reflex arc.
- Example is Golgi tendon reflex.

Polysynaptic reflexes:

- These reflexes involve many synapses in the reflex arc.
- Example is withdrawal reflex.

Muscle stretch reflex:

- The muscle stretch reflex is the contraction of a muscle in response to stretch of that muscle.
- It is a monosynaptic reflex.
- It occurs in all muscles of the body and is the primary mechanism for regulating muscle tone.
- Muscle tone is the tension present in all resting muscle.
- The best example of muscle stretch reflex is the knee jerk reflex.

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Knee jerk reflex:

- Tapping the patellar tendon causes the quadriceps to stretch.
- stretch of the quadriceps stimulates group I_a afferent fibers, which activate α-motor neurons that make the quadriceps contract.
- Contraction of the quadriceps causes extension of the leg at the knee.
- Afferent impulses simultaneously inhibit antagonist muscles through interneurons.

Clinical importance:

- The knee jerk is exaggerated in upper motor neuron lesion.
- Sluggish in lower motor neuron lesion.
- Becomes pendular in cerebellar lesion.

Golgi tendon organ:

- The Golgi tendon organ is an encapsulated sensory receptor through which muscle tendon fibers pass.
- About 10 to 15 muscle fibers are connected to each Golgi tendon organ.
- The Golgi tendon organ like primary nerve ending has both a dynamic response and a static response.
- Signals from tendon organ are transmitted through large, rapidly conducting type Ib nerve fibers that averages 16 µm in diameter.
- The dorsal spinocerebellar tracts carry information from both muscle spindles and Golgi tendon organs directly to the cerebellum at conduction velocities of 120 m/sec.
- When Golgi tendon organ is stimulated muscle will go for relaxation, while when muscle spindle is stimulated muscle will go for contraction.

Golgi tendon reflex or inverse muscle stretch reflex:

- It is a bisynaptic reflex.
- Active muscle contraction stimulates the Golgi tendon organs and group Ib afferent fibers.
- The group Ib fibers stimulates inhibitory interneurons in the spinal cord.
- These interneurons inhibit α-motor neurons and cause relaxation of the muscle that was originally contracted.
- At the same time, antagonist muscles are excited.
- This reflex provides negative feedback that prevents development of too much tension on the muscle, and prevents tearing of muscle and avulsion of tendon.

Flexor withdrawal reflex:

- It is a polysynaptic reflex.
- Results in contraction of flexor muscles and the relaxation of extensor muscles in that limb.
- It is a protective reflex in which a stimulus causes withdrawal of the stimulated limb.

Crossed extensor reflex:

- The crossed extensor reflex is a reflex in which the contralateral limb compensates for loss of support when the ipsilateral limb withdraws from painful stimulus in a withdrawal reflex,
- The flexor withdrawal reflex is accompanied by a crossed extensor reflex in which the contralateral limb is extended to support the body.
- For example, when one foot steps on a nail, the crossed extensor reflex shifts the body weight onto the other foot, protecting and withdrawing the foot on the nail.

Postural reflexes:

- Postural reflexes are responsible for the subconscious maintenance of the body posture, when movement and position is altered and they ensure that the body remains upright and aligned.

Positive supportive reflex:

- It is the first postural reflex to develop.
- In this reflex pressure on the footpad of the baby causes the limb to extend against the pressure applied to the foot and support the weight of the body.
- The locus of the pressure on the pad of the foot determines the direction in which the limb will extends, pressure on one side causes extension in that direction called magnet reaction.

Cord Righting reflex:

- When a spinal animal is laid on its side, it will make uncoordinated movements will try to raise itself to the standing position, this is called cord righting reflex.

Locomotive reflexes:

- These are involuntary modification of locomotor movements produced by sensory signals from receptors in the limbs and body.

Stepping reflex:

- The stepping reflex can be seen when a baby is held upright or when the baby feet are touching the ground, the baby tries to walk.
- Legs prance up and down as if baby is walking or dancing.
- This reflex is present at birth and disappears at 2 - 4 months of age.

Stumble reflex:

- If the top of the foot encounters an obstruction during forward thrust, the forward thrust will stop temporarily, then in rapid sequence the foot will be lifted higher and proceed forward to be placed over the obstruction, this is called stumble reflex.

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Reciprocal stepping of opposite limbs:

- stepping occurs in the forward direction in one limb, the opposite limb ordinarily moves backward. This effect results from reciprocal innervation b/w the two limbs.

Diagonal stepping of all four limbs- "Mark Time" reflex:

- stepping occurs diagonally b/w the forelimbs and hind-limbs. This is another manifestation of reciprocal innervation.

The Galloping reflex:

- In this reflex both forelimbs move backward with both hind limbs move forward. If stretch or pressure stimuli are applied equally to opposite limbs at the same time a galloping reflex will result, unequal stimulation on one side elicits the diagonal walking reflex.

Types of neural circuits:

Neural circuits found in the interneuron pool of cells of spinal cord are,

- Diverging circuits
- Converging circuits
- Repetitive discharge circuits

Reciprocal inhibition and reciprocal innervation:

- Excitation of a group of muscles is associated with inhibition of another group.
- When a stretch reflex excites one muscle, it inhibits the antagonist muscle at the same time.
- Reciprocal innervation refers to the neuronal circuit that causes the reciprocal relationship.

Scratch reflex:

- Scratch reflex is a spinal reflex that causes the person or an animal to scratch or rub the affected area.
- It is initiated by an itch or tickle sensation.

Mass reflex:

- An indiscriminate response of the body to a stimulus that all segmental reflexes can be elicited simultaneously is called mass reflex.
- This reflex can be elicited in patients with spinal cord lesions.
- When the skin is stimulated by pin pricks, there occurs evacuation of bowel or bladder, muscular spasm of legs, hypertension and sweating.

Significance:

- The patients suffering from spinal cord injuries are particularly trained to elicit mass reflex to evacuate bowel and bladder.

Muscle cramps:

- Any local irritating factor such as severe cold or lack of blood flow to the muscle can elicit pain or other sensory signals transmitted from muscle to spinal cord, causing reflex muscle contraction.
- Contraction stimulates sensory receptors more and a positive feedback mechanism occurs.
- So a small amount of initial irritation causes more and more contraction until a full-blown muscle cramp occurs.

Spinal shock:

- When spinal cord is transected in the neck, all cord functions including cord reflexes are blocked.
- The reason is that normal activity of the cord neuron depend on continual signals from higher centers transmitted through the reticulospinal tracts, vestibulispinal tracts and corticospiunal tracts.

Spinal functions affected during spinal shock:

- The arterial pressure falls.
- All skeletal muscle reflexes are blocked.
- The sacral reflexes for control of bladder and colon emptying are suppressed.

Clonus:

- Clonus is oscillation of muscle jerks and is present in upper motor neuron lesions.

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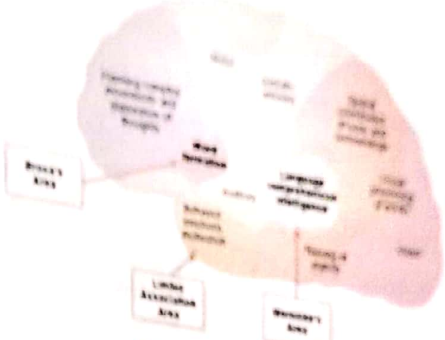
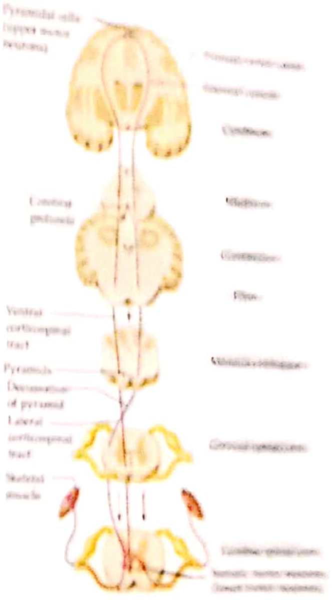
Motor cortex:

- Anterior to the central sulcus
- Divided into three areas,
- The primary motor cortex or Brodmann,s area 4 lies anterior to the central sulcus.
- The premotor area or Brodmann,s area 6 lies anterior to the primary motor cortex.
- The supplementary motor area lies mainly in the longitudinal fissure, causing bilateral movements.



Different Areas of cerebral cortex

Corticospinal or pyramidal tract:



Corticospinal tract

- Fiber of the corticospinal tract arises as axons of the pyramidal cells situated in 5th layer of cerebral cortex.
- Corticospinal tract originates 30% from primary motor cortex, 30% from premotor and supplementary motor cortex and 40% from somatosensory cortex.
- Corticospinal tract is concerned with voluntary, discrete and skilled movements.
- After leaving the cortex, the fibers pass through the posterior limb of the internal capsule. The tract then continuous through the midbrain, then forming pyramids of the medulla.
- At the junction of medulla and spinal cord, most of the fibers cross the midline at the decussation of the pyramids and enter the lateral white column of spinal cord to form lateral corticospinal tract. The remaining fibers do not cross in the decussation but descend in the anterior white column of spinal cord as anterior corticospinal tract.
- The anterior corticospinal tract fibers eventually cross the midline and terminate in the anterior gray column of spinal cord segments in the cervical and upper thoracic regions.
- The lateral corticospinal tract descends the length of the spinal cord, its fibers terminate in the anterior gray column of all spinal segments.

Lesions of corticospinal tract:

- Lesion of the corticospinal tract above pyramidal decussation, causes weakness on contralateral side of the body.
- Lesion of the corticospinal tract below pyramidal decussation, causes weakness on ipsilateral side of the body.

Extrapyramidal tracts:

Pontine reticulospinal tract:

- It originates in the pons and projects to the spinal cord.
- It excites anti-gravity muscles.

Medullary reticulospinal tract:

- It originates in the medulla and projects to the spinal cord.
- It inhibits anti-gravity muscles.

Tectospinal tract:

- It originates in the superior colliculus and projects to the spinal cord.
- It is concerned with reflex postural movements in response to visual stimuli.

Rubrospinal tract:

- It originates in the red nucleus and projects to the spinal cord.
- It facilitates the activity of flexor muscles and inhibits the activity of extensor muscles.

Vestibulospinal tract:

- It originates in vestibular nuclei and projects to the spinal cord.
- It facilitates the activity of extensor muscles and inhibits the activity of flexor muscles.

Spastic rigidity in the decerebrate animal:

- When the brainstem is sectioned below the midlevel of midbrain but the pontine, medullary reticular and vestibular systems are left intact, then decerebrate rigidity develops.
- This rigidity occurs only in the anti-gravity muscles.
- The cause of decerebrate rigidity is blockage of normal input to the medullary reticular nuclei from the cerebral cortex, the red nuclei and basal ganglia. Lacking this input, the medullary reticular inhibitor becomes non-functional, full over activity of the pontine excitatory system occurs and spastic rigidity develops.

Upper and lower motor neuron:

- An upper and lower motor neuron together form the basic neural circuit involved in the voluntary contraction of skeletal muscle everywhere in the body.
- Upper motor neuron innervates the lower motor neuron and the lower motor neuron innervates the skeletal muscle.

Upper motor neuron:

- UMN are group of all those neurons which originate at higher level than lower motor neuron and descend to lower motor neuron and alter the activity of LMN.

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- Cell bodies of UMN are found in the red nucleus, reticular formation, lateral vestibular nuclei of the brain stem and in cerebral cortex.
- Axons of these cortical neurons course in the corticospinal tract.

Lower motor neuron:

- Lower motor neurons are neurons coming out of CNS and connected to neuromuscular junction.
- LMN are found in the ventral horn of spinal cord and in cranial nerve nuclei in the brain stem.
- Axons of LMN of spinal nerves exit in a ventral root then join the spinal nerve and course in one of its branches to reach NMJ.
- Axons of LMN in brain stem exit in a cranial nerve.
- Both alpha and gamma motor neurons are LMN.

Upper and lower motor neuron lesion:

UMN Lesion	LMN Lesion
Hypertonia	Hypotonia or atonia
Hyper-reflexia	Areflexia
Babinski sign present	Babinski sign absent
Clonus present	Clonus absent
Spastic paresis	Flaccid paralysis
Disuse atrophy	Atrophy
Slight loss of power	Drastic change in power
Fasciculation absent	Fasciculation present
Fibrillation absent	Fibrillation present
Clonus present	Clonus absent
Paresis is ipsilateral and below the site of the lesion When lesion is below the decussation.	Paralysis is ipsilateral and and at the Level of the lesion.
Paresis is contralateral and below the site of the lesion When lesion is above the decussation.	

Vestibular system:

- The vestibular system provides balance, equilibrium and eye movements.
- It is composed of three semicircular canals and two chambers, the utricle and saccule.
- The semicircular canals detect angular acceleration.
- The utricle and saccule detect linear acceleration.

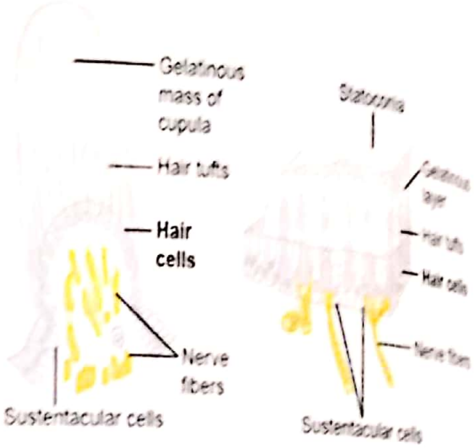
Semicircular canal:

- It is filled with endolymph.
- Each canal contains an enlargement called the ampulla.
- The ampulla has the receptor hair cells.
- Cilia on hair cells are embedded in a gelatinous tissue called the cupula.

- Smaller cilia are called sterocilia and a single long cilium is called the kinocilium.
- If the stereocilia are bent toward the kinocilium, the hair cells depolarize.
- If the stereocilia are bent away from the kinocilium, the hair cells hyperpolarize.

Macula:

- The utricle and saccule contain a small sensory area called macula.
- The macula of utricle lies in the horizontal plane.
- The macula of saccule lies in the vertical plane.
- Each macula is covered by a gelatinous layer in which small calcium carbonate crystals called statoconia are embedded.
- Macula also has cilia projected from hair cells.
- The statoconia have a specific gravity two to three times of surrounding fluid.
- The weight of statoconia bends the cilia in the direction of gravitational full.



Crista Ampullaris And Macula

Nystagmus:

- It is the rhythmic oscillations of the eyes slowly to one side followed by a rapid reflex movement in the opposite direction.
- The rapid reflex movement is used to describe the form of nystagmus.
- For example, a patient is said to have a nystagmus to the left if the rapid reflex movement is to the left and the slow phase is to the right.
- It may be caused by vestibular nerve or vestibular nucleus lesions.
- Treatment depends on patient condition and of the fact whether it is acquired or congenital.

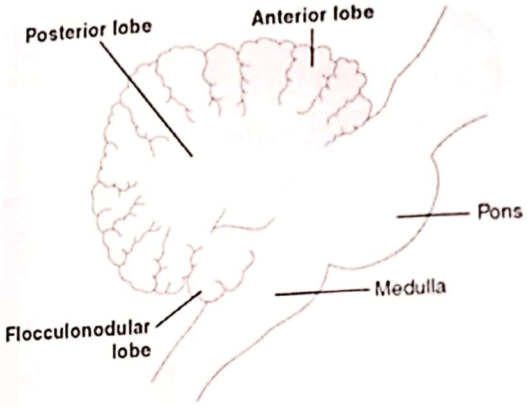
Cerebellum:

- It consists of two cerebellar hemispheres joined by a median vermis.
- It controls motor system ipsilaterally.
- It is concerned with tone, posture, balance and coordination of movements.
- Lesion of cerebellum does not cause paralysis of any muscle.
- Cerebellum develops from metencephalon.

Cerebellar peduncles:

There are three pairs of cerebellar peduncles,

- The superior cerebellar peduncles connect the cerebellum to the midbrain.
- The middle cerebellar peduncles connect the cerebellum to the pons.
- The inferior cerebellar peduncles connect the cerebellum to the medulla oblongata.



Lobes of the cerebellum

Lobes of the cerebellum:

Flocculonodular lobe:

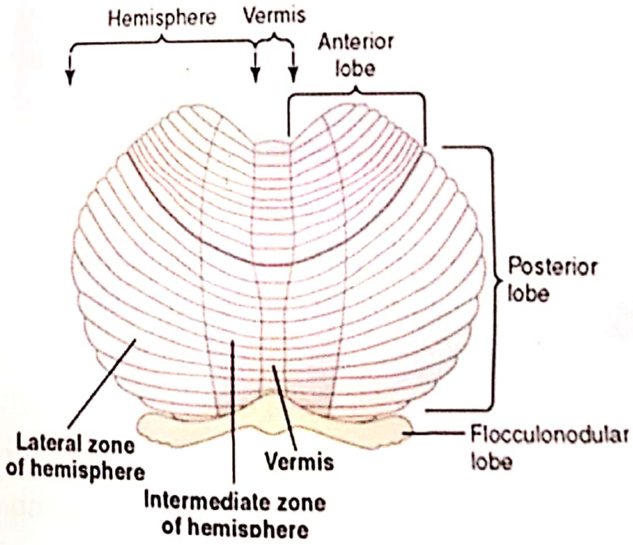
- Also called vestibulocerebellum.
- It is the oldest portion concerned with balance.

Anterior lobe:

- Also called spinocerebellum.
- It is concerned with tone.

Posterior lobe:

- Also called cerebro-cerebellum.
- It is concerned with coordination of movement.



Functional parts of the cerebellum

Functional areas of cerebellum:

Vermis of cerebellum:

- It control axial portion of the body.

Intermediate zone of cerebellum:

- It controls distal parts of the limbs, especially the hands and feet.

Lateral zone of cerebellum:

- It play important role in planning and coordination of movement.

Structure of cerebellum:

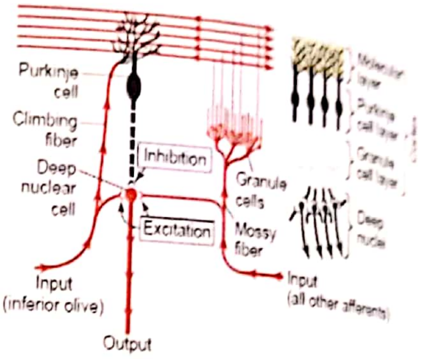
- The cerebellum is composed of an outer covering of gray matter called cortex and inner white matter.

Layers of the cerebellar cortex:

- Cerebellar cortex is divided into three layers, from outer to inner are,
- Molecular layer, Purkinji cell layer and Granular layer.
- Mnemonic to remember the sequence is "My Personal Garden".

Molecular layer:

- It is the outermost layer.
- Contains two types of neurons, the outer stellate cells and the inner basket cells.



Layers of cerebellum

Purkinji cell layer:

- It is the middle layer.
- Contains purkinji cells which are large Golgi type I neurons arranged in a single layer.

Granular layer:

- It is the innermost layer.
- Contains granule cells and Golgi cells.

Intra-cerebellar nuclei:

- Embedded in the white matter of each hemisphere are four masses of gray matter forming intracerebellar nuclei. From lateral to medial these are,
- Dentate, Emboliform, Globose and Fastigial.
- Mnemonic is "Do not Eat Greasy Food".
- Emboliform and globose nuclei are collectively called interposed nucleus.
- Fibers from the dentate, embiliform and globose nuclei leave the cerebellum through the superior cerebellar peduncle and from fastigial nucleus through the inferior cerebellar peduncle.

Input to the cerebellar cortex:

- The deep cerebellar nuclei receive afferent information from two sources, inhibitory from purkinji cells and excitatory from climbing and mossy fibers.

Climbing fibers:

- These fibers originate from inferior olivary nucleus.
- These fibers are excitatory.

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- Neurotransmitter is glutamate.
- One climbing fiber makes contact with 1 to 10 purkinji neurons.
- Result in complex spike.

Mossy fibers:

- These fibers originate from many areas in brain and spinal cord.
- These fibers are excitatory.
- Neurotransmitter is glutamate.
- One mossy fiber stimulates thousands of purkinji cells through granule cells.
- Result in simple spike.

Cerebellum cell types:

- The granule cells are the only excitatory neurons and release glutamate as the neurotransmitter.
- All other neurons in cerebellum purkinji, basket, stellate and Golgi cells are inhibitory and release GABA as the neurotransmitter.

Cerebellar Afferent Fibers:

- The afferent fibers enter the cerebellum through the middle and inferior cerebellar peduncles.

Corticopontocerebellar pathway:

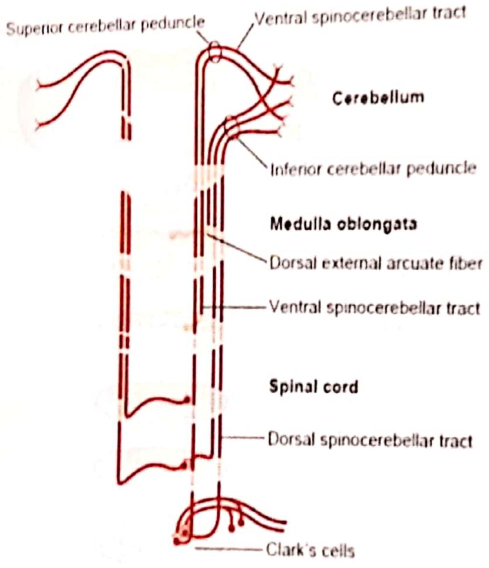
- It enters opposite cerebellum through middle cerebellar peduncles.
- Conveys control from cerebral cortex.

Anterior spinocerebellar tract:

- It enters the cerebellum through superior cerebellar peduncles.
- Conveys information from muscles and joints.

Posterior spinocerebellar tract:

- It enters the cerebellum through inferior cerebellar peduncles.
- Conveys information from muscles and joints.
- The spinocerebellar pathway transmits impulses at velocities of 120 m/sec.


Superior cerebellar peduncle
Ventral spinocerebellar tract
Cerebellum
Inferior cerebellar peduncle
Medulla oblongata
Dorsal external arcuate fiber
Ventral spinocerebellar tract
Spinal cord
Dorsal spinocerebellar tract
Clark's cells

Spinocerebellar tract

Olivocerebellar tract:

- It enters the opposite cerebellum through inferior cerebellar peduncles.
- These fibers terminate as climbing fibers in the cerebellar cortex.
- It relays information from cerebral cortex that projects to the inferior olive.

Reticulocerebellar rathway:

- It enters cerebellum through middle and inferior cerebellar peduncles.
- Conveys control from cerebral cortex.

Vestibulocerebellar pathway:

- It enters the cerebellum through inferior cerebellar peduncles.
- Conveys information of head position and movement.

Cuneocerebellar pathway:

- It enters the cerebellum through inferior cerebellar peduncles.
- Conveys information from muscles and joints of upper limb.

Cerebellar Efferent fibers:

- Output of cerebellum is from axons of deep cerebellar nuclei.
- They pass as axons of purkinji cells.
- Purkinji cells form functional unit of cerebellar cortex.

Globose-Emboliform-Rubral pathway:

- It travels through superior cerebellar peduncles.
- Influences ipsilateral motor activity.

Dentathalamic pathway:

- It travels through superior cerebellar peduncles.
- Influences ipsilateral motor activity.

Fastigial vestibular pathway:

- It travels through inferior cerebellar peduncles.
- Influences ipsilateral extensor muscle tone.

Fastigial reticular pathway:

- It travels through inferior cerebellar peduncles.
- Influences ipsilateral muscle tone.

Symptoms of cerebellar lesions:

Dysmetria:

- Dysmetria or past pointing is the inability to stop a movement at proper point.

Ataxia:

- It means uncoordinated movements.

Hypotonia:

- It means decreased muscle tone.

Dysdiadochokinesia:

- It is the inability to perform alternating movements rapidly.

Dysarthria:

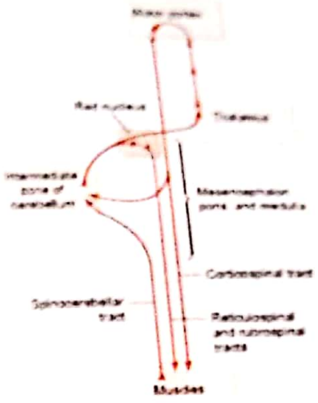
- Failure of progression in talking.

Intention tremor:

- It is a tremor amplified as the target is reached.

Nystagmus:

- It is a rhythmical oscillation of the eyes.


Motor cortex
Red nucleus
Thalamus
Intermediate zone of cerebellum
Mesencephalon, pons, and medulla
Corticospinal tract
Spinocerebellar tract
Reticulospinal and rubrospinal tracts
Muscles

Cerebral and cerebellar control of voluntary movements

The Basal Ganglia:

- It is a collection of masses of gray matter situated in each cerebral hemisphere.
- These include caudate nucleus, putamen, Globus pallidus, substantia nigra and subthalamic nucleus.
- The basal Ganglia play an important role in the control of posture and voluntary movement.
- Globus pallidus and putamen are collectively called lentiform nucleus.
- Caudate nucleus and lentiform nucleus are collectively called corpus straitum.
- Caudate nucleus and putamen are collectively called Neostraitum.

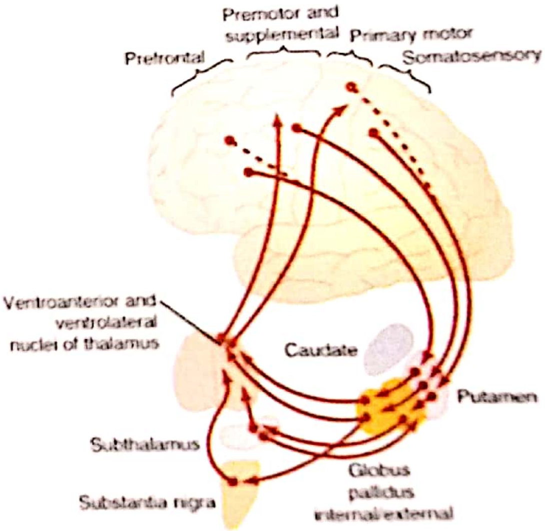
Abnormalities of Basal Ganglia:

Athetosis:

- It is slow, involuntary, writhing movements of distal segments of the limbs.
- It occurs due to lesion in the Globus pallidus.

Hemiballismus:

- It is sudden involuntary movement of limb on one side of the body.
- It occurs due to lesion in the subthalamus nucleus.


Premotor and supplemental
Primary motor
Prefrontal
Somatosensory
Ventroanterior and ventrolateral nuclei of thalamus
Caudate
Putamen
Subthalamus
Globus pallidus internal/external
Substantia nigra

Putamen circuit though the basal ganglia

Chorea:

- It is rapid, abnormal jerky or dancing movements.
- It occurs due to lesion in the putamen.

Parkinson disease:

- Its symptoms are, tremor, rigidity, akinesia and postural disturbances.
- It occurs due to lesion in the substantia nigra.
- It can be treated with a drug L-dopa.

Huntington,s disease:

- It is caused by a single gene defect on chromosome 4.
- In this disease, the GABA secreting, substance p secreting and neurons of the striatonigral inhibiting pathway degenerate.
- This causes the dopamine secreting neurons of the substantia nigra over
- Thus the nigrostraital pathway inhibits the caudate nucleus and inhibition produces abnormal movements.

IJT

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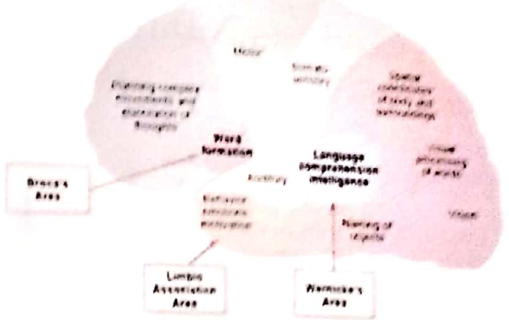
- In this disease, the GABA secreting, substance p secreting and acetylcholine secreting neurons of the striatonigral inhibiting pathway degenerate.
- This causes the dopamine secreting neurons of the substantia nigra over active.
- Thus the nigrostraital pathway inhibits the caudate nucleus and the putamen. Th inhibition produces abnormal movements.

Cerebral cortex:

- The cerebral cortex is composed of gray matter forms a complete covering of cerebral hemisphere. It is responsible for state of awareness, which is to respond to stimuli and interact with environment. Cerebral hemisphere control contralateral side of the body, so its lesion causes weakness and paralysis on contralateral side of the body.

Layers of cerebral cortex:

Cerebral cortex consist of six layers,


Motor
Somatic sensory
Planning complex movements and elaboration of thoughts
Spatial coordinates of body and surroundings
Word formation
Broca's Area
Language comprehension intelligence
Auditory
Visual processing of words
Behavior emotions motivation
Naming of objects
Visual
Limbic Association Area
Wernicke's Area

Cerebral cortex

- Molecular layer
- External granular layer
- External pyramidal layer
- Internal granular layer
- Internal pyramidal layer, this layer contains Betz cells which constitute 3% corticospinal fibers.
- Layer of polymorphic cells

Cortical Areas:

- Based on histological structure difference Brodmann divide cerebral cortex into 50 distinct areas called Brodmann,s areas.
- Primary motor area is Brodmann area 4.
- Secondary motor area is Brodmann area 6.
- Primary visual area is Brodmann area 17.
- Secondary visual area is Brodmann area 18 and 19.
- Primary auditory area is Brodmann area 41 and 42.
- Secondary auditory area is Brodmann area 22.
- Secondary olfactory area is Brodmann area 28.
- Motor speech area of Broca is Brodmann area 44 and 45.
- Primary somesthetic area is Brodmann area 3, 1 and 2.
- Somesthetic association area is Brodmann area 5 and 7.

Prosopagnosia:

- It is the inability to recognize faces.
- It can be caused by lesions in occipital lobes and anterior temporal lobe.

Personal neglect syndrome:

- Lesions of the posterior parietal cortex produce agnosia, which is the inability to recognize objects.
- Also such a person will avoid left side of the body for the performance of tasks, which is called personal neglect syndrome.

Wernicke area:

- It is the sensory speech area located in the left dominant hemisphere.
- Its role is in understanding of written and spoken language.

Arcuate fasciculus:

- The Wernicke area is connected to the broca,s area by a bundle of nerve fibers called arcuate fasciculus.

Left hemisphere dominancy:

- About 95% of population is left hemisphere dominant for speech and motor functions.

Expressive aphasia:

- Lesions of broca,s area result in loss of ability to produce speech.
- The patient can write and understand words.

Receptive aphasia:

- Lesions of Wernicke area produce loss of ability to understand spoken and written words.
- Speech is normal.

Global aphasia:

- Lesion involving both Broca and Wernicke areas results in loss of production of speech and understanding spoken and written words.

Conductive aphasia:

- Lesion of arcuate fasciculus results in conductive aphasia in which the patient is unable to repeat words or phrases.

Angular gyrus:

- It is the visual interpretation area.
- Its lesions divide the pathway b/w visual association area and Wernicke area results in alexia (unable to read) or agraphia (unable to write).

Corpus callosum:

- It connects two cerebral hemispheres.

Anterior commissure:

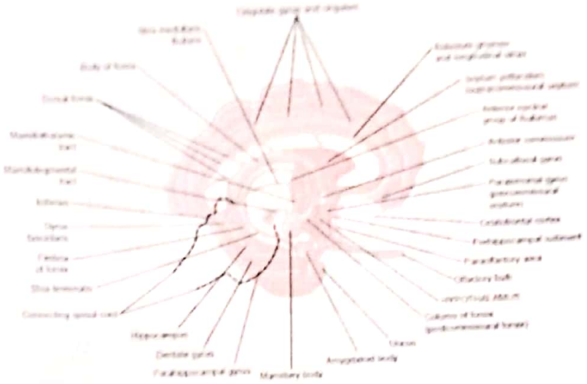
- It is b/w two temporal lobes.

Posterior commissure:

- It is b/w two pretectal nuclei.

Limbic system:

- It is a set of structures in the brain that deal with emotions, behavior and memory.
- It is composed of four main parts,
- The hippocampus
- The Amygdala
- The Thalamus
- The Hypothalamus



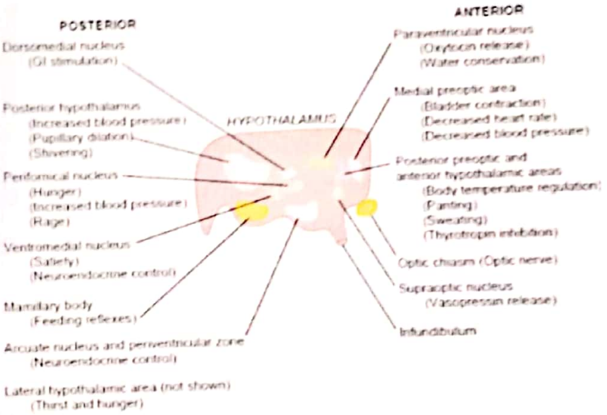
Limbic system

Hippocampus:

- It is a part of the limbic system.
- It is located in the medial temporal lobe of the brain.
- It is mainly responsible for formation of long term memory.

Amygdala:

- It is a part of the limbic system.
- It is located in the temporal lobe just anterior to the hippocampus.
- Play important role in emotion and behavior.


POSTERIOR
ANTERIOR
HYPOTHALAMUS
Dorsomedial nucleus (GI stimulation)
Posterior hypothalamus (Increased blood pressure) (Pupillary dilation) (Shivering)
Perifornical nucleus (Hunger) (Increased blood pressure) (Rage)
Ventromedial nucleus (Satiety) (Neuroendocrine control)
Mamillary body (Feeding reflexes)
Arcuate nucleus and periventricular zone (Neuroendocrine control)
Lateral hypothalamic area (not shown) (Thirst and hunger)
Paraventricular nucleus (Oxytocin release) (Water conservation)
Medial preoptic area (Bladder contraction) (Decreased heart rate) (Decreased blood pressure)
Posterior preoptic and anterior hypothalamic areas (Body temperature regulation) (Panting) (Sweating) (Thyrotropin inhibition)
Optic chiasm (Optic nerve)
Supraoptic nucleus (Vasopressin release)
Infundibulum

Control Centers of the Hypothalamus

Amnesia:

- It is loss of memory.

Types of amnesia:

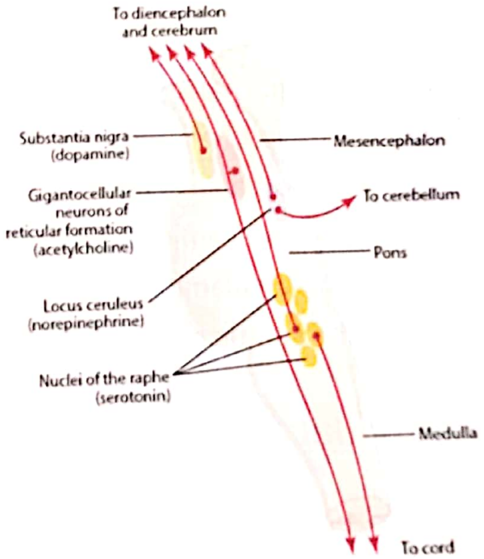
- There are two types of amnesia,

Anterograde amnesia:

- Loss of the ability to create new memories after the event that caused amnesia.
- Cause is damage to the hippocampus.

Retrograde amnesia:

- Unable to recall events that occurred before the development of amnesia.
- May be able to memorize new things.
- Cause is lesion of hippocampus but specifically thalamus lesion lead to retrograde amnesia.


To diencephalon and cerebrum
Substantia nigra (dopamine)
Mesencephalon
Gigantocellular neurons of reticular formation (acetylcholine)
To cerebellum
Pons
Locus ceruleus (norepinephrine)
Nuclei of the raphe (serotonin)
Medulla
To cord

Multiple centers in the brain stem

Kluver-Bucy syndrome:

- Results from lesion of amygdaloid nucleus.
- Patient may present with,
- Compulsive eating
- Hyper-sexuality
- Insertion of inappropriate objects into the mouth.
- Docility

Thalamus:

- It is a mass of gray matter that forms the major part of the diencephalon.
- Inter-thalamic connection is a band of gray matter that connects two thalami.
- Stratum zonale, a thin layer of white matter covering the superior surface of thalamus.
- External medullary lamina is a thin layer of white matter covering the lateral surface of thalamus.
- Internal medullary lamina is a Y-shaped sheet of white matter that divides the gray matter of thalamus into medial and lateral halves.
- The thalamus is composed of different nuclei, each serve a unique role, ranging from relaying sensory and motor signals, as well as regulation of consciousness and alertness.
- All sensory information except olfaction relays on thalamus.
- Lesions of the thalamus cause disability on contralateral side of the body b/c the thalamus receives sensory impulses from opposite side of the body.

Hypothalamus:

- It is a part of the hypothalamus.
- Located below the thalamus and above the pituitary gland.
- Its main function is to maintain the homeostasis of the body.

Hypothalamic nuclei:

- Supra-optic nucleus synthesizes vasopressin or ADH.
- Para-ventricular nucleus synthesizes oxytocin.
- Pre-optic and anterior nuclei control parasympathetic system.
- Posterior and lateral nuclei control sympathetic system.
- Anterior hypothalamic nuclei regulate temperature, show response to heat.
- Posterior hypothalamic nuclei regulate temperature, show response to cold.
- Lateral hypothalamic nucleus is hunger center, initiate eating.
- Medial hypothalamic nucleus is satiety center, inhibit eating.
- Lateral hypothalamic nucleus is thirst center, increase water intake.
- Supra-chiasmatic nucleus controls circadian rhythms.

Reticular formation:

- It is a set of interconnected nuclei that are located throughout the brainstem.
- It modulates the control of motor and sensory systems.
- It plays crucial role in maintaining behavioral arousal and consciousness.
- Medial forebrain bundle connect limbic system with brainstem reticular formation.

Division of reticular formation:

- The locus ceruleus secrete norepinephrine which plays an important role in causing dreaming thus lead to rapid eye movement sleep.
- Substantia nigra secrete dopamine, its destruction cause Parkinson,s disease.
- The raphe nuclei secrete serotonin which plays an inhibitory role to cause normal sleep.
- The Gigantocellular neurons secrete acetylcholine which acts as an excitatory neurotransmitter.

Coma:

- It is a state of unconsciousness from which a person cannot be aroused

Sleep:

- It is a state of unconsciousness from which a person can be aroused.

Centers causing sleep:

- Raphe nuclei whose fibers endings secrete serotonin.
- Nucleus of the tractus solitaries.
- Suprachismatic nucleus of hypothalamus.
- Muramyl peptide, a substance causing sleep.

Neurotransmitter of sleep:

- Acetylcholine
- Serotonin

Intense wakefulness:

- Lesion of raphe nuclei and supra-chiasmatic nuclei cause intense wakefulness.

Narcolepsy:

- A sleep disorder characterized by overwhelming daytime drowsiness and sudden attacks of sleep.
- Orexin or hypocretin is a neuropeptide produced by neurons in the hypothalamus that regulates arousal and wakefulness.
- Lesions of orexin producing neurons or defective orexin receptors cause narcolepsy.

Insomnia:

- It is a sleep disorder that makes it hard to fall asleep.

Sleep apnea:

- A sleep disorder in which breathing repeatedly stops and starts.
- The patient will snore loudly and feel tired even after a full night sleep.

Restless legs syndrome:

- A sleep disorder causes unpleasant sensations in the legs and irresistible urge to move the legs.

Importance of sleep:

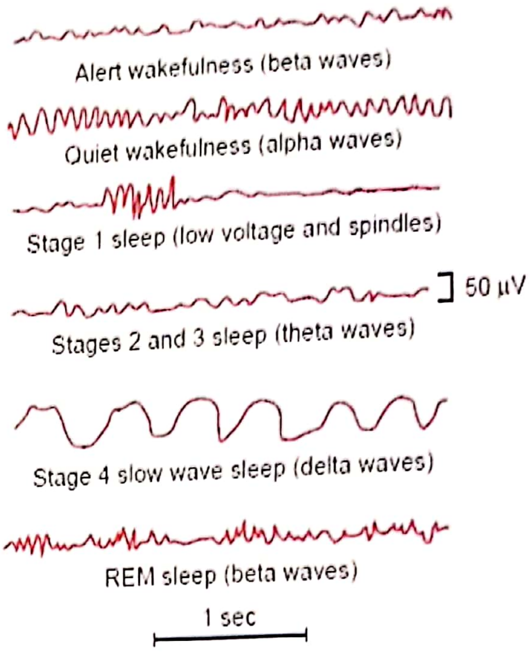
- Restore natural balances among neuronal centers.
- Improves memory.
- Clearance of metabolic wastes.
- Conservation of metabolic energy.
- Stay at a healthy weight.

Types of sleep:

There are two types of sleep,

Rapid eye movement sleep:

- Also called paradoxical or desynchronzed sleep.
- Characterized by rapid movement of the eyes.
- Dreamfull sleep.
- Occurs in episodes and each episode occurs after every 90 minutes, lasting for 5 to 30 minutes.
- Occupy 25% of sleep time.
- Difficult to arouse the person.
- Muscle tone depressed.
- Heart rate and respiratory rate become irregular.
- The brain is quite active.
- Acetylcholine causes REM sleep.
- Brain waves are irregular and of high frequency.



Different Types of Brian waves

Slow wave sleep:

- Also called deep sleep.
- Brain waves are strong and of low frequency.
- Characterized by Delta waves.
- Restful sleep.
- Respiratory rate, blood pressure and basal metabolic rate decreases.
- Dreamless sleep, sometimes nightmares do occur.
- Serotonin causes slow wave sleep.

Brain waves:

Alpha waves:

- Rhythmical waves.
- Occur at frequency b/w 8 and 13 cycles/sec.
- Found in the ECG of all healthy adults when they are awake and in a quiet, resting state of cerebration.
- Occur most intensely in the occipital region.
- Voltage is about 50 mv.
- Disappear during deep sleep.
- Not occur in cerebral cortex without cortical connections with the thalamus.

Beta waves:

- Occur at frequency greater than 14 cycles/sec and as high as 80 cycles/sec.
- Recorded from parietal and frontal regions during specific activation of these areas.
- Involved in conscious thought, logical thinking and focusing.
- Alert wakefulness is characterized by Beta waves.

Theta waves:

- Frequency b/w 4 and 7 cycles/sec.
- Occur in the parietal and temporal regions in children.
- Occur in adults during emotional stress or psychomotor states.
- Occur in degenerative brain states.

Delta waves:

- Frequency less than 3.5 cycles/sec.
- Voltage two to four times greater than other types of brain waves.
- Occur in deep sleep, in infancy and in serious organic brain diseases.
- Occur in surgical anesthesia and in animals with subcortical transection.

Seizure:

- A sudden alteration of behavior due to a temporary change in the electrical activity of the brain.

Epilepsy:

- It is a disorder of the brain characterized by repeated seizures.

Types of epileptic seizures:

- There are two main types, Focal seizures and Generalized seizures.

Focal or partial epileptic seizures:

- Localized to a focal area of one cerebral hemisphere.

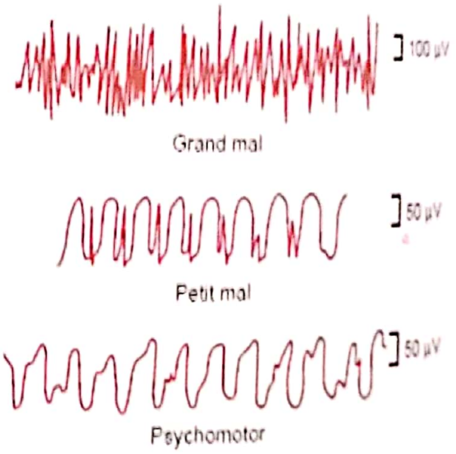
Classification of partial seizures:

Simple partial seizure:

- When seizure does not affect awareness.

Complex partial seizures:

- When seizure impaired awareness.



Electroencephalograms in different types of epilepsy

Jacksonian march:

- Also called jacksonian seizures
- The tingling or twitching begins in a small area and then marches or spread to a larger area of the body.

Generalized seizures:

- It occurs when the abnormal electrical activity causing a seizure begins in both cerebral hemispheres.

Classification of generalized seizures:

Generalized Tonic-clonic or Generalized Grand Mall seizures:

- Characterized by an abrupt loss of consciousness and extreme neuronal discharge throughout the brain.
- In the tonic phase the body becomes rigid and in the clonic phase there is uncontrolled jerking.
- The patient cry, bites his tongue, difficulty in breathing and may urinate or defecate.
- Seizure lasts for one or two minutes.
- High voltage, high frequency discharges occur over the entire cortex.

Absence seizures or Petit Mall seizures:

- It causes the patient to blank eyes or stares into space for a few seconds.
- Most common in children.
- Do not cause long term problems.
- It involves the thalamocortical brain activating system.
- The brain wave pattern is "spike and dome" pattern.

Postictal period:

- The time after the seizure prior to the return of normal neurological function is called postictal period.

Treatment of epilepsy:

- Many medications are used in the treatment of epilepsy and seizures,
- Carbamazepine
- Phenytoin
- Ethosuximide
- Phenobarbital
- Valproate
- Topiramate

Depression:

- It is a constant feeling of sadness and loss of interest, which stops the person from doing normal activities.
- It is caused by diminished activity of norepinephrine and serotonin secreting neurons.
- Treatment is,
- Monoamine oxidase inhibitors which block destruction of norepinephrine and serotonin.
- Antidepressants such as imipramine and amitriptyline which block reuptake of norepinephrine and serotonin by nerve endings.

Bipolar disorder:

- Also known as manic depression.
- It is a mental disorder characterized by periods of depression and periods of abnormally elevated mood refer as mania.
- During mania an individual feels abnormally energetic and happy.

Schizophrenia:

- It is a serious mental disorder that results in delusions, hallucinations, disorganized speech, trouble with thinking and lack of motivation.
- Caused by exaggerated function of the dopamine system.
- It can be treated with chlorpromazine, haloperidol and thiothixene.

Alzheimer,s disease:

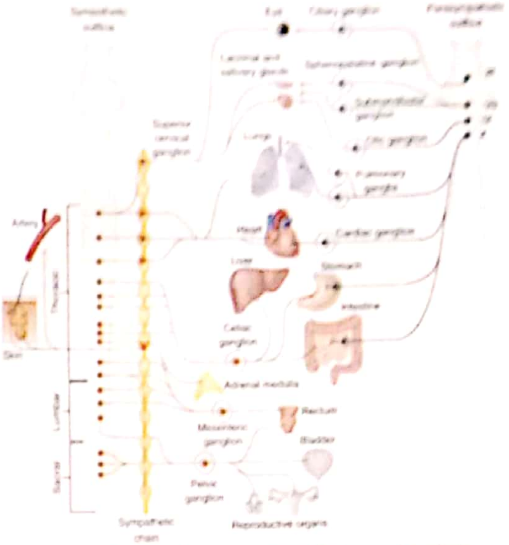
- It is a degenerative brain disorder which is the most common form of dementia.
- Usually starts in late middle age.
- Results in progressive memory loss, impaired thinking and change in personality and mood.
- Neurofibrillary tangles and plagues containing beta-amyloid cells are present.
- Loss of acetylcholine neurons occur in the Meynert nucleus.
- Treatment is acetylcholinesterase inhibitors such as Donepezil and Rivastigmine.

Autonomic nervous system:

- It is the part of nervous system that innervates smooth muscles, cardiac muscles and Glands of the body.

Organization:

- The autonomic nervous system is divided into two parts,
- Sympathetic nervous system
- Para-sympathetic nervous system



Sympathetic and parasympathetic Nervous system

Sympathetic nervous system:

- It is fight or flight system
- Prepare the body for emergency
- Its outflow is thoracolumbar, from spinal cord segments T_1-T_2.
- Its ganglia are pre-vertebral and paravertebral. e.g: celiac and superior mesenteric ganglia.
- Preganglionic fibers are short.
- Postganglionic fibers are long.
- Its preganglionic fibers liberate acetylcholine.
- Its most postganglionic fibers liberate nor-epinephrine while on sweat glands acetylcholine.
- Its action is widespread.
- Its receptors are α_1, α_2, β_1 and β_2 adrenergic.
- Ratio of preganglionic to postganglionic fibers is 1:10.
- Preganglionic fibers are myelinated B fibers.
- Postganglionic fibers are unmyelinated C fibers.

Parasympathetic nervous system:

- It is rest and digest system.
- Conserve and restore energy.
- Its outflow is craniosacral, from iii, vii, ix and x cranial nerves and S_2, S_3 and S_4 spinal cord segments.
- Its ganglia are close to visceraor within plexus. e.g: ciliary and otic ganglia.
- Preganglionic fibers are long.
- Postganglionic fibers are short.
- Its preganglionic fibers liberate acetylcholine.
- Its postganglionic fibers liberate acetylcholine.
- Its action is discrete.
- Its receptors are muscarinic and nicotinic cholinergic.
- Ratio of preganglionic to postganglionic fibers is 1:3.
- Preganglionic fibers are myelinated B fibers.
- Postganglionic fibers are unmyelinated C fibers.

Adrenal Medulla:

- It is composed of chromaffin cells which secrete two types of hormones,
- About 80% epinephrine.
- About 20% nor-epinephrine.

Pheochromocytoma:

- It is benign tumor of adrenal gland.
- Excessive secretion of epinephrine and nor-epinephrine occur.
- Symptoms are Hypertension, tachycardia, sweating and headache.
- It can be treated with phenoxybenzamine.

Cholinergic receptors:

- These are the receptors on the surfaces of cells that get activated when they bind a type of neurotransmitter called acetylcholine.

Types of cholinergic receptors:

- There are two types,

Nicotinic receptors:

- Responsive to acetylcholine and Nicotine.
- Ionotropic receptors or ligand gated ion channels.
- Cause opening of sodium/potassium channels.
- No second messengers.
- Cause excitation.

Types:

- Have sub types,

N_N:

- Found in the autonomic ganglia, adrenal medulla and CNS.

N_M:

- Found in Neuromuscular junction.

Muscarinic receptors:

- Responsive to acetylcholine and muscarine.
- Metabotropic receptors or G-protein coupled receptors.
- Use second messengers as their signaling mechanism.
- Found in heart, smooth muscles and glands.
- Inhibitory in the heart.
- Excitatory in smooth muscles and glands.

Types:

- Have sub types,
- **M1:** These are G_q coupled found in Gastric glands, Autonomic ganglia and CNS.
- **M_2:** These are G_i coupled found in the heart, cause inhibition.
- **M_3:** These are G_q coupled found in smooth muscles, exocrine glands and endothelial cells.
- **M4 and M_5:** Found in CNS.

Adrenergic receptors:

- These are membrane bound G-protein coupled receptors that are targets of nor-epinephrine and epinephrine.

Types of adrenergic receptors:

α_1 receptors:

- These are G_q protein bound excitatory receptors which increase IP_3, DAG and Ca^{++}.
- Found in smooth muscles.
- Cause vasoconstriction.

α_2 receptors:

- These are G_i protein bound inhibitory receptors which decrease CAMP level.
- Found in presynaptic neurons, pancreas, platelets and CNS.
- Decrease neurotransmitter and insulin release.

β_1 receptors:

- These are G_s protein bound stimulatory receptors which increase CAMP level.
- Found in heart, juxtaglomerular cells and adipose tissue.
- Increase heart strength, renin release and lipolysis.

β_2 receptors:

- These are Gs protein bound stimulatory receptors which increase CAMP level.
- Found in vascular smooth muscles.
- Cause vasodilation.

β_3 receptors:

- These are Gs protein bound stimulatory receptors which increase CAMP level.
- Found in adipose tissue.
- Increase lipolysis.

Effect of Autonomic nervous system on body organs:

Organ	sympathetic action	parasympathetic action
Eye (pupil)	Dilation	Constriction
Eye (ciliary muscle)	Relaxation	Contraction
Lacrimal and salivary glands	Reduce secretion	Increase secretion
Sweat glands	Increase secretion	No effect
Nasal glands	Reduce secretion	Increase secretion
Heart	Increase rate	Decrease rate
Lung bronchioles	Dilation	constriction
Gut wall	Decrease motility	Increase motility
Gut sphincter	Constriction	Relaxation
Bladder detrusor	Relaxation	Contraction
Bladder sphincter	Constriction	Relaxation
Penis	Ejaculation	Erection
Gallbladder and bile ducts	Relaxation	Contraction
Kidney	Decrease output	No effect
Fat cells	Increase lipolysis	No effect
Bronchial arteries	Constriction	Dilation
Apocrine glands	Thick, odoriferous secretion	No effect
Systemic blood vessels	Mostly constricted	Mostly no effect
Gastric glands	Decrease secretion	Increase secretion
Piloerector muscles	contraction	No effect

Pharmacology of the autonomic nervous system:

Cholinergic agonists:

- Pilocarpine and physostigmine are cholinergic agonists act on muscarinic receotors.

Cholinergic antagonists:

- Atropine and scopolamine are muscarinic receptor antagonists.

Ganglion blockers:

- Hexamethonium and mecamylamine block both sympathetic and parasympathetic transmission through ganglia.

Adrenergic agonists:

- Phenylephrine (α_1) and salbutamol (β_2) are adrenergic receptors agonists.

Adrenergic antagonists:

- Phenoxybenzamine and phentolamine block both α_1 and α_2 adrenergic receptors.
- Prazosin and terazosin block α_1 adrenergic receptors.
- Yohimbine block α_2 adrenergic receptors
- Propranolol blocks β_1 and β_2 adrenergic receptors.
- Atenolol and metoprolol block β_1 adrenergic receptors.

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Brain meninges:

- The brain in the skull is surrounded by three protective membranes called meninges.
- From outer to inner these layers are,
- Dura matter
- Arachnoid matter
- Pia matter

Ventricular system:

- The ventricles are four fluid filled cavities located within the brain.
- These are lined with ependyma and are filled with CSF.
- There are two lateral ventricles, the third ventricle and the fourth ventricle.

Lateral ventricles:

- Located in cerebral hemisphere.
- Communicate with third ventricle through inter-ventricular foramen or foramen of Monro.

Third ventricle:

- Located in the diencephalon.
- Communicate with fourth ventricle through cerebral aqueduct or aqueduct of sylvius.

Fourth ventricle:

- Located anterior to cerebellum and posterior to pons and superior half of medulla.
- Communicate with central canal of lower medulla, spinal cord and subarachnoid space through a single median opening called foramen of magendie and two lateral openings called foramen of luschka.

Central canal:

- It opens superiorly into the fourth ventricle.
- Inferiorly it extends throughout the length of spinal cord and in the conus medullaris expands to form the terminal ventricle.
- It is closed at its lower end, filled with CSF and is lined with ependyma.

Subarachnoid space:

It is the space b/w the arachnoid matter and pia matter and is present where theses meninges envelop the brain and spinal cord.

Choroid plexus:

- It is a vascular fringe composed of pia matter covered with ependyma.
- Produce CSF.
- The cerebral aqueduct and central canal do not have choroid plexus.
- Blood supply of choroid plexus of lateral ventricles and third ventricle is from choroidal branches of internal carotid and basilar arteries.
- Blood supply of choroid plexus of 4th ventricle is from posterior inferior cerebellar artery.

Cerebrospinal fluid:

- It is a fluid found in the ventricles and in subarachnoid space around the brain and spinal cord.
- It is secreted by choroid plexus.
- Its reabsorption occurs in the arachnoid granulations.
- Volume is 150 ml.
- Rate of production is 0.5 ml/min.
- Pressure is 60 - 150 mm of H_2O.
- Appearance is colorless.
- Number of lymphocytes are 0 - 3 cells/mm^3.
- It protects and nourishes the CNS.

Composition:

- Protein - 15 - 45 mg/100 ml.
- Glucose - 50 - 85 mg/100 ml.
- Chloride - 720 - 750 mg/100 ml.

Blood brain barrier:

- It is the barrier b/w the cerebral capillary blood and the interstitial fluid of the brain.
- The structures that contribute blood brain barrier are,
- Capillary endothelial cells with tight junctions.
- Basement membrane.
- Foot processes of astrocytes.

Hydrocephalus:

- It is a condition in which accumulation of CSF occurs within the brain and causes increased pressure inside the skull.

Types of hydrocephalus:

Communicating hydrocephalus:

- It occurs when the flow of CSF is blocked after it exits the ventricles.

Non-communicating hydrocephalus:

- It occurs when the flow of CSF is blocked along one or more of the narrow passages connecting the ventricles.

Blood supply of the brain:

- The brain is supplied by the two internal carotid and two vertebral arteries.

Internal carotid artery:

- It begins at the bifurcation of the common carotid artery.

Internal carotid artery branches:

Ophthalmic artery:

- It supplies the structures of the orbit.

Posterior communicating artery:

- Acts as an anastomosing artery in the circle of willis.

Choroidal artery:

- It supplies lateral geniculate body, optic tract and internal capsule.

Anterior cerebral artery:

- Supplies medial surface of cerebral cortex and leg area on the lateral cerebral cortex.

Middle cerebral artery:

- Supplies lateral cerebral cortex except leg area.

Vertebral artery:

- A branch of the first part of the subclavian artery.

Vertebral artery branches:

Meningeal branches:

- Supply dura in the posterior cranial fossa.

Anterior spinal artery:

- Supply the spinal cord.

Posterior spinal artery:

- Supply the spinal cord.

Posterior inferior cerebellar artery:

- Supplies the cerebellum.

Medullary arteries:

- Supply the medulla oblongata.

Basilar artery:

- It is formed by the union of two vertebral arteries.

Basilar artery branches:

Pontine arteries:

- Supplies pons.

Labyrinthine artery:

- Supplies internal artery.

Anterior inferior cerebellar artery:

- Supplies the anterior and inferior parts of cerebellum.

Superior cerebellar artery:

- Supplies the superior surface of cerebellum.

Posterior cerebral artery:

- Supplies the occipital cortex.

Circle of willis:

- It lies in the interpeduncular fossa at the base of the brain.
- It is formed by the anastomosis of two internal carotid and two vertebral arteries.
- The anterior communicating, anterior cerebral, internal carotid, posterior communicating, posterior cerebral and basilar arteries all contribute to the circle of willis.

Intracranial hemorrhages:

- Four varieties of intracranial hemorrhage occurs,

Epidural hemorrhage:

- It results from damage to anterior division of middle meningeal artery.
- Epidural hematoma is lens shaped.

Subdural hemorrhage:

- It results from damage to superior cerebral veins.
- Subdural hematoma is crescent shaped.

Subarachnoid hemorrhage:

- It results from damage to circle of willis.

Cerebral hemorrhage:

- It results from damage to lenticulostriate artery, a branch of the middle cerebral artery. This hemorrhage involves the corticobulbar and corticospinal fibers and produce hemiplegia on contralateral side of the body.

Part-V

ENDOCRINOLOGY
AND
REPRODUCTION

Cytokines:

- These are peptides secreted by cells into the extracellular fluid.
- Function as autocrines, paracrines or endocrine hormone.
- e.g: interleukin and leptin.

Autocrine:

- Secreted by cells into the extracellular fluid.
- Affect function of the same cells that produce them.

Paracrine:

- Secreted by cells into the extracellular fluid.
- Affect neighboring target cells of a different type.

Hormone:

- Secreted by glands.
- Transported to a distance where it acts on target tissues.

Types of hormones:

- There are three types,

Peptides:

- Hypothalamic regulatory hormones, pituitary hormones, insulin, glucagon and parathyroid hormones.

Steroids:

- Cortisol, aldosterone, estrogen, progesterone and testosterone.

Amines or derivatives of A.A tyrosine:

- Thyroid hormones, epinephrine and norepinephrine.

Note:

- There are no known polysaccharide or nucleic acid hormones.

Storage of hormones:

- Peptides are synthesized on rough endoplasmic reticulum and are stored in vesicles.
- Steroids are synthesized from cholesterol as needed and are not stored.
- Amine hormones are derived from A.A tyrosine and are stored.

Concentration of hormones in the blood:

- It range from 1 Pico gram to a few micro grams per ml of blood.

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Regulation of hormone secretion:

Negative feedback:

- It prevents over activity of hormone system.
- A hormone has a negative feedback effect to prevent over secretion of the hormone or over activity at the target tissue.
- e.g: insulin secretion.

Positive feedback:

- It occurs when the biological actions of the hormone causes additional secretion of the hormone.
- e.g: Surge of luteinizing hormone before ovulation.

Cyclic variations in hormone release:

- Hormone secretion is also influenced by seasonal changes, various stages of development and aging, the diurnal cycle and sleep.
- e.g: the secretion of growth hormone increased during the early period of sleep but is reduced during the latter stages of sleep.

Transport of hormones in the blood:

- Water soluble hormones, peptides and catecholamine are dissolved in the plasma and transported from their sites of synthesis to target tissues in free form.
- Lipid soluble hormones steroids and thyroid hormones circulate in the blood while bound to plasma protein.

Hormone receptors:

- Hormone receptors are large proteins and have different locations for different hormones.
- Peptide hormones and catecholamine receptors are found on the surface of cell membrane.
- Steroid hormones receptors are found in the cytoplasm.
- Thyroid hormones receptors are found in the nucleus and are located in direct association with one or more chromosomes

Regulation of hormone receptors:

- The number of receptors in a target cell does not remain constant.

Down regulation of receptors:

- Some hormones decrease the number or affinity of receptors for itself or for another hormone and cellular activity is reduced, which is called down regulation of receptors.

Up-regulation of receptors:

- Some hormones increase the number or affinity of receptors for itself or for another hormone and cellular activity is increased which is called up-regulation of receptors.

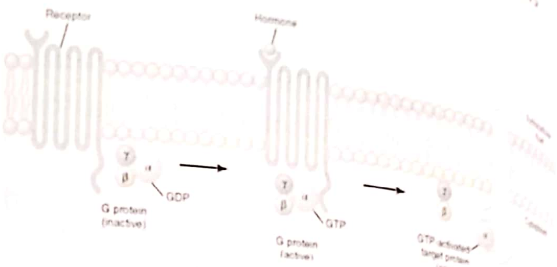
Mechanism of action of receptors:

- A hormone affects its target tissues by first activating its receptors and the activated receptors then initiates the hormonal effects.
- There are different types of interactions,

Ion channel linked receptors:

- These receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through the channel.
- Plays role in synaptic transmission.

G-Protein linked receptors:

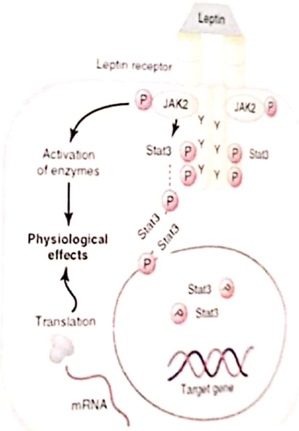


Mechanism f activation of a G protein-coupled receptor

- G-protein linked receptors bind a ligand and activate a membrane protein called G- protein, which then interacts with an ion channel or an enzyme such as adenylyl cyclase or phospholipase C which alter cell function.
- All G-protein linked receptors have seven trans-membrane segments.
- G-proteins are trimeric molecule consist of alpha, beta and gamma subunits.
- In inactive state G- protein binds GDP on the alpha subunit.
- When a signaling molecule binds to G- protein coupled receptors, a GDP molecule associated with the alpha subunit is exchanged for GTP. The alpha subunit dissociates from the trimeric complex and triggers the cellular response.
- Hydrolysis of GTP to GDP terminates the signal.

Enzyme linked receptors:

- These are cell surface receptors with intracellular domains that are associated with an enzyme.
- These receptors pass through the membrane only once.
- When a ligand binds to the receptor, a signal is transfused through the membrane and activates the enzyme, which sets off a chain of events with in the cell that eventually leads to a response.
- Example is tyrosine kinase receptor.



An Enzyme linked receptors

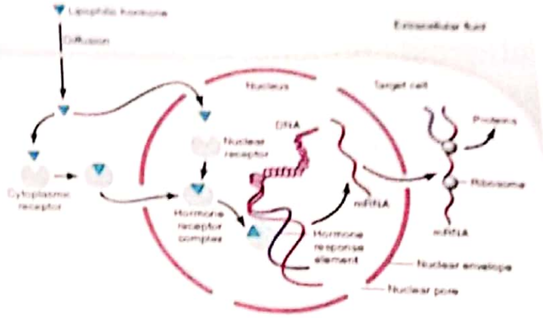
Intracellular hormone receptors:

- Intracellular receptors are located inside the cell rather than on cell membrane.

- Thyroid and steroid hormones receptors are intracellular receptors.
- When the hormone enters the cell and binds to receptors and activates the receptors.
- The activated receptors initiate the hormonal effects, which is the activation of transcription and then translation process on the ribosomes to form new proteins.

Hormones that use tyrosine kinase Mechanism:

- Growth hormone
- Insulin
- Erythropoietin
- Fibroblast growth factor
- Insulin like growth factor - 1
- Leptin
- prolactin



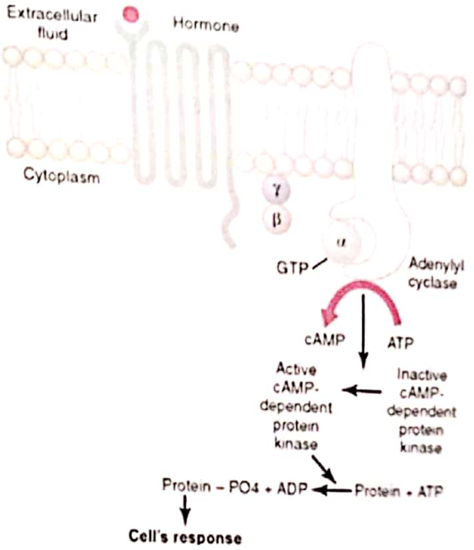
Intracellular Hormone Receptor

Hormones that use nuclear receptor mechanism:

- Androgens
- Estrogens
- Glucocorticoids
- Mineralocorticoids
- Vitamin D3
- Thyroid hormones
- Retinoic acid

Adenylyl Cyclase- CAMP second messenger system:

- G-protein linked receptor binds a ligand and activates a membrane protein called G- protein.
- The G-protein subunit alpha releases its GDP, which is replaced by GTP.
- The alpha subunit dissociates from the G- complex and binds to adenylyl cyclase.
- Activated adenylyl cyclase produces CAMP, by conversion of ATP to CAMP.
- CAMP phosphorylates protein kinase A which causes specific actions.
- At last CAMP is degraded to 5'- AMP by phosphodiesterse.



Mechanism of action of cAMP

Hormones that use CAMP second messenger mechanism:

- Catecholamines
- ADH (V_2 receptor)
- Adrenocorticotropic hormone

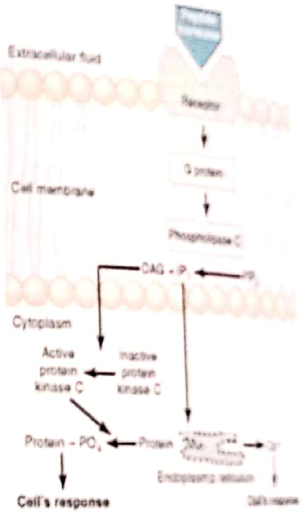
- HCG
- Glucagon
- Somatostatin
- FSH and LH
- Corticotropin releasing hormone
- TSH
- Parathyroid hormone
- Melanocyte stimulating hormone
- Calcitonin
- Growth hormone releasing hormone

Hormones that use CGMP second messenger system:

- CGMP is synthesized from GTP using the enzyme Guanylyl cyclase.
- CGMP serves as the second messenger for,
- Atrial natriuretic peptide
- Nitric oxide

Phospholipase - C second messenger system:

- Hormones activate trans-membrane receptors that activate the enzyme phospholipase- C
- This enzyme catalyzes the breakdown of phosphatidylinositol bi-phosphate into two different second messenger products, inositol triphosphate and Diacylglycerol.
- The inositol triphosphate mobilizes the calcium ions from mitochondria and endoplasmic reticulum and the calcium ions then have their own second messenger effects.
- Diacylglycerol activates the enzyme protein kinase C, which phosphorylates large number of proteins leading to cells response.
- The lipid portion of diacylglycerol is arachidonic acid which is precursor for the prostaglandins that cause multiple effects in tissues.



Phospholipase-C Second messenger system

Hormones that use phospholipase - C second messenger system:

- Angiotensin II
- ADH (V_1 receptor)
- CCK
- Oxytocin
- Thyrotropin releasing hormone

Calcium calmodulin second messenger system:

- Hormones bind to the receptor.
- Open calcium ion channels and release calcium ions from endoplasmic reticulum.
- Calcium acts as a second messenger in two way,
  i. Calcium binds to an enzyme and activates it, to produce physiological action.
  ii. Calcium binds to calcium binding protein such as calmodulin to produce physiological action.
- Calmodulin has four calcium binding sites.
- The normal calcium ion concentration in most cells of the body is 10 to 10 mol/L.

Pituitary gland:

- ➢ It controls secretion of other endocrine glands, so called master gland.
- ➢ Also called hypophysis.
- ➢ Located in the sella turcica, connected to the hypothalamus by hypophysial stalk.

Lobes of pituitary gland:

- ➢ Anterior pituitary also called adenohypophysis, originates from Rathke,s pouch.
- ➢ Posterior pituitary also called neurohypophysis, originates from diencephalon.
- ➢ B/w these two lobes is a small avascular zone called pars intermedia.

Anterior pituitary cells:

Cell type	Hormone secreted	% of anterior pituitary cells
Somatotropes	growth hormone	50%
Corticotropes	ACTH	20%
Gonadotropes	FSH, LH	10%
Lactotropes	Prolactin	15%
Thyrotropes	TSH	5%

Hormones of anterior pituitary gland:

Growth hormone or somatotropin:

- ➢ Single chain of 199 A.A.
- ➢ Molecular weight is 22005.
- ➢ The only pituitary hormone which do not act on other endocrine gland.
- ➢ Stimulates body growth, lipolysis and inhibits action of insulin.

Adrenocorticotropic hormone:

- ➢ Single chain of 39 A.A.
- ➢ Stimulates production of glucocorticoids and androgens by the adrenal cortex.

Thyroid stimulating hormone:

- ➢ Glycoprotein of two subunits, α - chain of 89 A.A and β - chain of 112 A.A.
- ➢ Stimulates production of thyroid hormones.

Follicle stimulating hormone:

- ➢ Glycoprotein of two subunits, α- chain of 89 A.A and β- chain 0f 112 A.A.
- ➢ Stimulates development of ovarian follicles and regulates spermatogenesis in testis.

Luteinizing hormone:

- ➢ Glycoprotein of two subunits, α- chain of 89 A.A and β- chain 0f 112 A.A.
- ➢ Causes ovulation, stimulates estrogen and progesterone production by the ovary and stimulates testosterone production by the testis.

Prolactin:

- Single chain of 198 A.A.
- Stimulates production and secretion of milk.

Hypothalamus controls pituitary secretion:

- All pituitary secretions are controlled by either hormonal or nervous signals from hypothalamus.
- Secretion from anterior pituitary is controlled by hormones called hypothalamic releasing and hypothalamic inhibitory hormones, secreted with in the hypothalamus and conducted to the anterior pituitary through hypothalamic-hypophysial portal blood vessels.
- For most of anterior pituitary hormones, hypothalamic hormones are releasing but for prolactin a hypothalamic inhibitory hormone exerts more control.
- Secretion from posterior pituitary gland is controlled by nerve signals that originate in the hypothalamus and terminate in the posterior pituitary.

Hypothalamic hormones that control anterior pituitary secretion:

Thyrotropin releasing hormone:

- Peptide of 3 A.A.
- Stimulates secretion of TSH.

Gonadotropin releasing hormone:

- Single chain of 10 A.A.
- Stimulates secretion of FSH and LH.

Corticotropin releasing hormone:

- Single chain of 41 A.A.
- Stimulates secretion of ACTH.

Growth hormone releasing hormone:

- Single chain of 44 A.A.
- Stimulates secretion of growth hormone.

Growth hormone inhibitory hormone or somaostatin:

- Single chain of 14 A.A.
- Inhibits secretion of growth hormone.

Prolactin inhibiting hormone:

- It is dopamine (a catecholamine).
- Inhibits synthesis and secretion of prolactin.

Physiological functions of growth hormone:

- Increases protein synthesis in muscle and increases lean body mass.
- Increases lipolysis.
- Decreases glucose uptake into cells b/c of induced insulin resistance.
- Increases production of somatomedins or insulin like growth factor.
- Promotes increase in sizes of cells and increase mitosis.

Factors that stimulate or inhibit growth hormone secretion:

- Growth hormone is secreted in a pulsatile pattern, increasing and decreasing.

Factors that stimulate growth hormone secretion:	Factors that decrease growth hormone secretion
Decreased blood glucose	increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Starvation, protein deficiency	Aging
Trauma, stress, excitement, Exercise	Obesity
Growth hormone releasing hormone	Growth hormone inhibitory hormone
Testosterone, Estrogen	somatomedins
Deep sleep	

Somatomedins:

- Growth hormone exerts much of its effect through intermediate substances called somatomedins.
- Growth hormone causes the liver to form somatomedins.
- Somatomedin effects on growth are similar to the effects of insulin on growth, so somatomedins are also called insulin like growth factors.
- Somatomedin- C is most important, also called insulin like growth factor-1.
- Somatomedi - C has molecular weight of 7500.
- Growth hormones attach weakly to plasma proteins and have half life in blood less than 20 minutes.
- Somatomedin- C attaches strongly to carrier proteins and have half life of 20 hours.
- The pygmies of Africa have a congenital inability to synthesize somatomedin- c. Their plasma concentration of growth hormone is either normal or high. They have diminished amount of somatomedin-c which accounts for the small stature of these people.
- The Levi-Lorain dwarf also has this problem.

Clinical disorders of growth hormone secretion:

Panhypothyroidism:

- In this disorder decreased secretion of all anterior pituitary hormones occur.
- General effects are hypothyroidism, depressed production of glucocorticoids and gonadotropic hormone.

- xcept for abnormal sexual functions, the patient can be treated by administering adrenocortical and thyroid hormones.

Dwarfism:

- It occurs due to deficiency of growth hormone in children.
- Patient has short stature.

Gigantism:

- It occurs due to hyper-secretion of growth hormone in children.
- Excessive linear growth occurs.

Acromegaly:

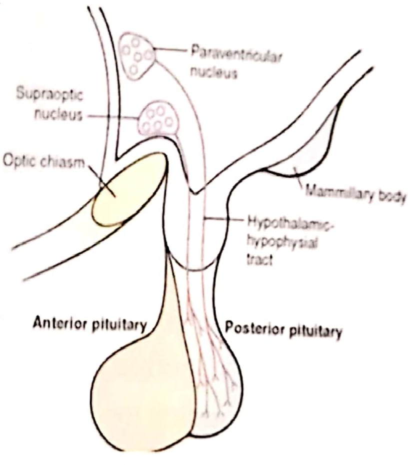
- It occurs due to hyper-secretion of growth hormone in adults.
- Enlargement of hands, feet, forehead, jaw and nose occur.

Hormones of posterior pituitary gland:

- Posterior pituitary secretes two types of hormones,

Antidiuretic hormone:

- Also called vasopressin.
- Synthesized in supra optic nuclei of hypothalamus.
- Polypeptide consists of 9 A.A.
- Regulates osmolarity of body fluids by increasing water permeability of the late distal tubules and collecting ducts.



Pituitary Gland

Oxytocin:

- Also called love hormone.
- Synthesized in the paraventricular nuclei of hypothalamus.
- Polypeptide consists of 9 A.A.
- Causes contraction of the pregnant uterus during delivery.
- Helps in milk ejection by the breast.

Note:

Both ADH and oxytocin are identical, except that in ADH phenylalanine and arginine replace isoleucine and leucine of the oxytocin molecule.

Sheehan syndrome:

- It affects women who lose large amount of blood during childbirth or have severe low blood pressure during or after childbirth, which can deprive the body of oxygen.
- This lack of oxygen causes ischemic infarction of pregnant enlarged pituitary gland.
- May Cause panhypopituitarism.
- Failure of lactation occurs.

Thyroid gland:

- Endocrine gland.
- Located below the larynx on each side of and anterior to the trachea.
- Composed of closed follicles that are filled with colloid and are lined with cuboida epithelial cells.
- Major constituent of colloid is a glycoprotein thyroglobulin which contains thyro hormones.

Thyroid hormones:

- Thyroxine and triiodothyronine which increase the metabolic rate of the body.
- Calcitonin that contributes to regulation of plasma calcium ion concentration.

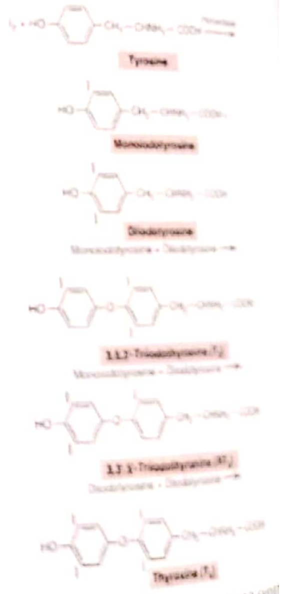
Thyroid hormone synthesis

Iodide pump:

- It is in the basal membrane of thyroid cell, co-transports one iodide ion along with two sodium ions into the cell.
- Energy for transporting iodide against a concentration gradient comes from Na^+- K^+ ATPase pump.
- Iodide is transported out of the thyroid cells across the apical membrane into the follicle by a chloride - iodide ion counter transporter molecule called pendrin.

Thyroglobulin:

- A glycoprotein having molecular weight of 335,000.
- Synthesize and secreted by endoplasmic reticulum and Golgi apparatus of thyroid cells into the follicles.
- Each molecule of thyroglobulin consist of 70 tyrosine A.A.
- Major substrate that combine with iodine to form thyroid hormones.
- After synthesis of thyroid hormones, it remains part of the thyroglobulin and stored in follicles.



Chemistry of Thyroid hormone synt

Synthesis of thyroid hormones:

- Each step in the synthesis of thyroid hormones is stimulated by thyroid stimulating hormone.

Oxidation of the iodide pump:

- First step in the synthesis of thyroid hormones is conversion of iodide ions to an oxidize form of iodine.
- Oxidation of iodide is catalyzed by peroxidase.

Organification of thyroglobulin:

- Binding of iodine with the thyroglobulin molecule is called organification of thyroglobulin.
- Iodine binds with about one-sixth of the tyrosine A.A within the thyroglobulin.
- Initial products are monoiodotyrosine and diiodotyrosine.

Coupling:

- Peroxidase also catalyze coupling of iodinated tyrosine.
- When two molecules of diiodityrosine are joined, tetraiodotyrosine (T_4) is formed.
- When one molecule of monoiodotyrosine couples with one diiodotyrosine, triiodotyrosine (T_3) is formed.
- When one molecule of diiodotyrosine couples with one monoiodityrosine ,reverse T_3 (RT_3) is formed which is inactive.
- T_4 or thyroxine is 3, 5, 3, 5′-tetraiodothyronine.
- T_3 or triiodothronine is 3, 5, 3′-triiodothyronine.
- RT_3 is 3, 3′, 5′-triiodothyronine.

Storage of thyroid hormone:

- Stored as iodinated thyroglobulin in the follicles.

Secretion of thyroid hormones:

- Proteases within the lysosomes of thyroid cells digest the thyroglobulin molecules and release throxine and triiodothyronine in free form.
- Iodinated tyrosine in the thyroglobulin that do not form thyroid hormones remain monoiodotyrosine and diiodotyrosine. Their iodine is cleaved from the deiodinase enzyme which makes it available for recycling.

Transport of thyroid hormones in blood:

- Thyroid hormones are transported in plasma protein bound form.
- Bound mainly with globulin and less with prealbumiun and albumin.

Activation and degradation of thyroid hormones:

- Triiodothyronine is about four times as potent as thyroxine but present in smaller quantity and for short time as compared with thyroxine.
- Most of the thyroxine is converted to triiodothyronine in peripheral tissue by the enzyme 5′-monodeiodinase.

Thyroxine:

- Contains four iodine atoms per molecule.
- 90% of thyroid hormones.
- Higher affinity towards binding protein.
- Half life is 6 days.
- Less potent.

Triiodothyronine:

- Contains three iodine atoms per molecule.
- 10% of thyroid hormones.
- Less affinity towards binding protein.
- Half life is 1 day.
- Four times as potent as thyroxine.

Regulation of thyroid hormone secretion:

- TRH from hypothalamus stimulates secretion of TSH from the anterior pituitary gland.
- TSH a glycoprotein having MW of 28,000 increases synthesis and secretion of thyroid hormones.
- Increased thyroid hormone in the body fluids decreases secretion of TSH by the anterior pituitary through negative feedback.

Antithyroid Drugs:

- These substances suppresses thyroid secretion,
- Propylthiouracil
- Methimazole
- Carbimazole
- Iodine

Functions of thyroid hormones:

- Increases cardiac output and tissue blood flow.
- Increases heart rate and heart strength.
- Increases basal metabolic rate.
- Increases respiration and oxygen consumption.
- Increases number and activity of mitochondria.
- Increases activity of Na^+-K^+ ATPase.
- Increases glucose absorption, Gluconeogenesis and Glycogenolysis.
- Increases lipolysis.
- Increases protein synthesis.
- Increases gastrointestinal motility.
- Promote growth and development of brain during fetal and initial postnatal life.

Tests for thyroid function:

- Measurement of concentration of TSH in the blood.
- Measurement of concentration of free thyroxine in the blood.
- Detection of antibodies in autoimmune thyroid disease.

Grave's disease:

- Common form of hyperthyroidism.
- Autoimmune disease in which thyroid stimulating immunoglobulins are formed against the TSH receptor in the thyroid gland.
- These antibodies bind with the same receptors that bind TSH, resulting hyperthyroidism.
- High level of thyroid hormone suppresses TSH secretion by anterior pituitary gland.

Exophthalmos:

- Also called proptosis.
- It is an abnormal protrusion of the eyeball.
- Common in people with hyperthyroidism.
- May stretches optic nerve and damage vision.

Thyrotoxicosis:

- Excess thyroid hormone action at the tissue level due to high circulating thyroid hormone secretion.
- Thyroxine level is high and TSH is suppressed.

Hashimoto's disease:

- Autoimmune disorder.
- Destroy thyroid gland.
- Cause hypothyroidism.

Goiter:

- It is an abnormal enlargement of thyroid gland.

Types of goiter:

Endemic goiter:

- Caused by iodine deficiency.

Nontoxic goiter:

- Cause is unknown.

Myxedema:

- Develops in person with hypothyroidism.
- Patient shows bagginess under eyes and swelling of face.
- Edema is non-pitting type.

Cretinism:

- A condition characterized by physical deformity and learning difficulties.

Causes:

- Caused by congenital thyroid deficiency.

Symptoms:

- Stunted growth
- Mental retardation
- Abnormal bone growth
- Large tongue
- Constipation
- Excessive sleep

Differences b/w hyperthyroidism and hypothyroidism:

Hyperthyroidism	Hypothyroidism
Increased basal metabolic rate	Decreased basal metabolic rate
Increased lipolysis	Decreased lipolysis
Hyper-glycaemia	Hypo-glycaemia
Weight loss	Weight gain
Increased heart rate	Decreased heart rate
Nervousness, anxiety	Lethargy, mental retardation
Weakness, muscle fatigue	Stiffness, muscle fatigue
Insomnia	Extreme somnolence
Increased appetite, diarrhea	Decreased appetite, constipation
Menstrual irregularity, decreased fertility	Menorrhagia, infertility
Exophthalmos	Puffy face, large tongue, Myxedema
Intolerance to heat	Intolerance to cold
Negative nitrogen balance	Positive nitrogen balance
Treatment is propylthiouracil and Surgical removal of thyroid gland	Treatment is thyroid hormone replacement

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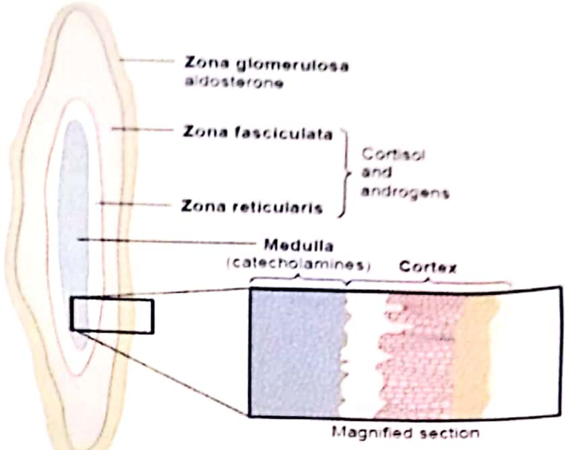
Adrenal Gland:

- Two in number each weighs about 4 g.
- Located at the superior poles of the kidneys.
- Each gland composed two parts, the adrenal medulla and the adrenal cortex.

Adrenal medulla:

- It is the central 20% of the adrenal gland.
- Functionally related to the sympathetic nervous system.
- Secretes epinephrine and nor-epinephrine
- These hormones cause same effects as direct stimulation of sympathetic nerves.



Secretion of adrenocortical hormones

Adrenal cortex:

- It secretes corticosteroids or adrenocortical hormones.
- Corticosteroids include mineralocorticoids, glucocorticoids and androgen.
- Aldosterone is the principal mineralocorticoid.
- Cortisol is the principal glucocorticoid.

Synthesis of adrenocortical hormones:

- These hormones are steroids synthesized from cholesterol.
- About 80% of cholesterol used for steroid synthesis is provided by low density lipoproteins.
- Once cholesterol enters the cell, it is delivered to the mitochondria, where it is cleaved by the enzyme cholesterol desmolase to form pregnenolone, this is the rate limiting step in the formation of adrenal steroids.
- Both **ACTH** which stimulates cortisol secretion and **angiotensin ii** which stimulates aldosterone secretion, increase the conversion of cholesterol to pregnenolone. All steps for synthesis of adrenal steroids occur in mitochondria and endoplasmic reticulum.

Secretion of adrenocortical hormones:

- The adrenal cortex is composed of three layers,

Zona glomerulosa:

- Outer zone of adrenal cortex.
- Constitutes about 15% of adrenal cortex.
- Secretes aldosterone b/c it contains aldosterone synthase.
- Its secretion is controlled by extracellular fluid concentration of angiotensin ii and potassium, both stimulate aldosterone secretion.

Zona fasciculate:

- Middle and white zone.
- Constitute about 75% of adrenal cortex.
- Secrete glucocorticoids and androgens.
- Its secretion is regulated by by ACTH.

Zona reticularis:

- Inner zone of adrenal cortex.
- Constitute about 10% of adrenal cortex.
- Secretes glucocorticoids and androgens.
- Its secretion is regulated by ACTH.

Mineralocorticoids:

Aldostrone:

- Very potent, accounts for about 90% of all mineralocorticoid activity.

Deoxycorticosterone:

- 1/30 times as potent as aldosterone.

9α-Fluorocortisol:

- Synthetic, more potent than aldosterone.

Corticosterone, cortisol and cortisone:

- Have slight mineralocorticoid activity.

Glucocorticoids:

Cortisol:

- Very potent, accounts for about 95% of all glucocorticoid activity.

Corticosterone:

- Less potent than cortisol, accounts for 4% of glucocorticoid activity.

Cortisone:

- As potent as cortisol.

Prednisolone:

- Synthetic, four times as potent as cortisol.

Methylprednisolone:

- Synthetic, five times as potent as cortisol.

Dexamethasone:

- Synthetic, 30 times as potent as cortisol, having zero mineralocorticoid activity.

Transport of adrenocortical hormone:

- The concentration of cortisol in blood averages 12 μg/100 ml and secretory rate is 15 mg/day. About 90% of cortisol in plasma binds to plasma protein especially globulin and to a lesser extent albumin. Due to this high degree of binding cortisol has long Half life of 60-90 minutes.
- The concentration of aldosterone in blood is 6ng/100 ml and secretory rate is 0.15mg/day. About 60% of aldosterone in plasma binds with plasma protein and about 40% is in free form. So aldosterone has short Half life of about 20 minutes.

Aldosterone:

- Mineralocorticoid activity of aldosterone is about 3000 times that of cortisol.
- Plasma concentration of cortisol is about 2000 times that of aldosterone.
- Aldosterone increases renal tubular sodium reabsorption and secretion of potassium and hydrogen ions.
- Aldosterone increases extracellular fluid volume and atrial pressure but has only a small effect on plasma sodium concentration.
- Excess aldosterone causes hypokalemia, alkalosis and muscle weakness.
- Deficiency of aldosterone causes hyperkalemia, acidity and cardiac toxicity such as arrhythmia.

Regulation of aldosterone secretion:

- Increased extracellular fluid potassium ion increases aldosterone secretion.
- Increased angiotensin II in extracellular fluid increases aldosterone secretion.
- Increased extracellular sodium ion very slightly decreases aldosterone secretion.
- ACTH is necessary for aldosterone secretion but has little effect in most physiological conditions.

Apparent mineralocorticoid excess syndrome:

- Cortisol can also bind to mineralocorticoid receptors with high affinity.
- Renal epithelial cells express the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD_2) which prevents cortisol from activating mineralocorticoid receptors.
- Patient with genetic deficiency of 11β-HSD2 activity, cortisol may have mineralocorticoids effects and the patient has the same conditions as a patient with excess aldosterone secretion except that plasma aldosterone levels are very low.
- This condition is called apparent mineralocorticoid excess syndrome.

Physiological functions of cortisol:

- Stimulate gluconeogenesis, antagonizes insulin effects and decreased glucose utilization by cells so cause a condition called adrenal diabetes, in which blood glucose level is elevated.
- Decreased protein synthesis and increased degradation of cellular protein but increased hepatic protein synthesis.
- Increased lipolysis and promotes mobilization of free fatty acids.
- Cortisol is important in resisting stress and inflammation, so block inflammatory response to allergic reactions and prevent shock or death as a result of anaphylaxis.
- Cortisol attenuates fever by inhibiting release of interleukin-1 from white blood cells which is the excitant of the hypothalamic temperature control system.
- Excess cortisol causes obesity in which excess deposition of fat occurs in the chest and head regions of the body giving a "buffalo like tarso" and a rounded "moon face".

Circadian rhythm of cortisol secretion:

- There is circadian rhythm in the secretion of cortisol, because the secretory rates of CRF, ACTH and cortisol are high in the early morning but low in the late evening.

Stress hormones:

There are five stress hormones. All stress hormones raise blood glucose level.

- Cortisol
- Thyroid hormone
- Growth hormone
- Glucagon
- Epinephrine

Androgens:

- Secreted by adrenal cortex.
- Contribute to growth and reproduction in both men and women.
- Causes growth of pubic and axillary hair in female.

Addison's disease:

- Also called adrenal insufficiency.
- Decreased production of cortisol by adrenal cortex.
- Characterized by hypoglycemia, weakness, fatigue, anorexia, weight loss, hypotension, hyponatremia, hyperkalemia, metabolic acidosis and hyperpigmentation of skin and mucous membrane.
- Treatment is administration of glucocorticoids and mineralocorticoids.

Cushing syndrome:

- Excessive production of cortisol occurs from adrenal cortex.

- Characterized by hyperglycemia, hypertension, hypokalemia, obesity giving a "buffalo like tarso" and hirsutism.
- Treatment is metyrapone and ketoconazole drugs.

Cushing disease:

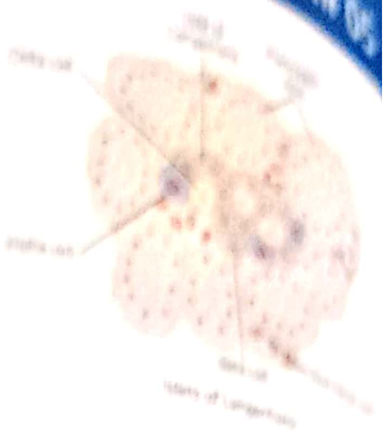
- Excessive production of cortisol occur secondary to excess secretion of ACTH by the anterior pituitary or adenoma of the anterior pituitary.
- Symptoms are same as that of cushing syndrome.
- Treatment is surgical removal of ACTH secreting tumor.

Primary aldosteronism:

- Also called conn's syndrome.
- Excessive production of aldosterone due to tumor of zona glomerulosa cells.
- Characterized by hypokalemia, metabolic alkalosis, hypertension and decreased renin secretion.
- Treatment is surgical removal of aldosterone secreting tumor and spironolactone drug.

Adrenogenital syndrome:

- Excessive production of androgen occur.
- Due to deficiency of 21β-hydroxylase enzyme.
- Characterized by female virilization, growth of beard, deeper voice and growth of clitoris to resemble penis.
- Treatment is administration of glucocorticoids and mineralocorticoids which suppress adrenal androgen secretion.



Pancreas:

- Heterocrine gland composed of exocrine and endocrine cells.

Acini:

- Exocrine cells.
- Secrete digestive enzymes into the duodenum.

Islets of Langerhans:

- Endocrine cells.
- Secrete insulin and glucagon into the blood.

Major types of cells of islets of Langerhans:

Beta cells:

- Constitute 60% of islet cells.
- Lie in the center of islet.
- Secrete insulin and amylase.
- Blood first flow to capillaries in the center of islet and pick up insulin.

Alpha cells:

- Constitute 25% of islet cell.
- Lie in the periphery of islet.
- Secrete glucagon.

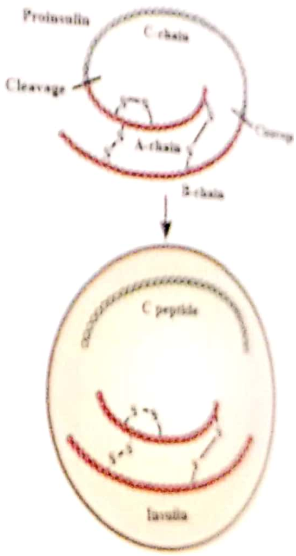
Delta cells:

- Constitute 10% of islet cells.
- Interspersed between alpha and beta cells.
- Secrete somatostatin.

PP cells:

- Not major type present in small number.
- Secrete pancreatic polypeptides.

Insulin:

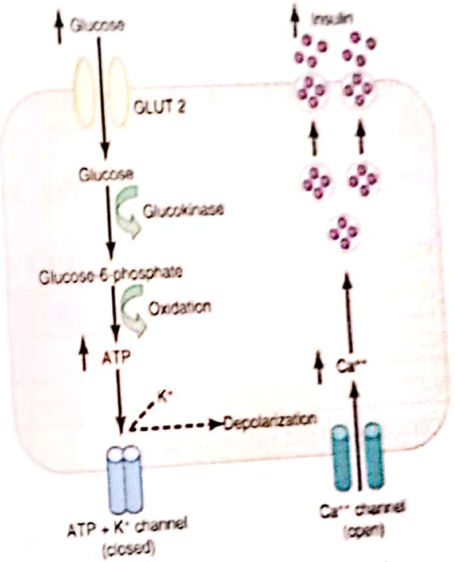


Pro Insulin and Insulin

- Peptide hormone of 51 A.A.
- Composed of two A.A chains.
- A - chain composed of 21 and B - chain composed of 30 A.A.
- The chains are connected to each other by two disulphide bond.
- In insulin two disulphide bonds are interchain and one is intrachain.
- When two chains are split apart, functional activity of insulin is lost.
- Insulin has molecular weight of 5808.
- Hypoglycemic hormone.
- Insulin was discovered by Banting and Best in 1922.

Insulin Synthesis and Secretion:

- On chromosome 11 short arm there are genes for insulin.
- Insulin is synthesized in beta cells, first forming pre- pro -insulin having MW of 11500 and have signal sequence or initial segment.
- Pre-pro-insulin is cleaved in endoplasmic reticulum, lost initial segment forming pro-insulin having molecular weight of 9000 and consist of A,B, and C peptide chains.
- Pro-insulin is cleaved in Golgi apparatus to form insulin and C peptide.
- Insulin is composed of A and B chains.
- The insulin and C peptide are packaged in secretory vesicles in association with Zinc.
- The insulin and C peptide are secreted in equimolar amounts.
- C-peptide is marker of endogenous insulin secretion.
- Patients with type-1 diabetes who are unable to produce insulin will have decreased level of C-peptide.
- The pro-insulin and C-peptide have no insulin activity.
- When insulin is secreted into blood, it circulates in an unbound form.
- Insulin has a plasma half life of about 6 minutes.
- When exogenous insulin is administered to a diabetic patient, it decreases C-peptide level.

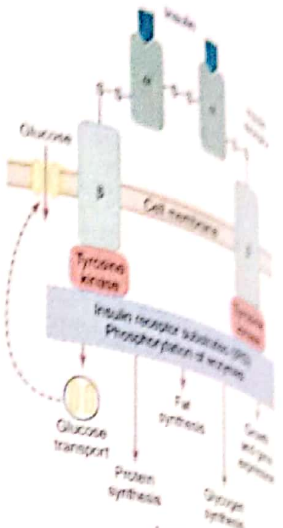


Mechanism of insulin secretion

Mechanism of insulin secretion:

- Blood glucose is the primary controller of insulin secretion.
- The Beta cells of pancreas have GLUT-2 glucose transporter which permit glucose influx.
- When glucose enters the cell, it is phosphorylated to glucose-6-phosphate by glucokinase.
- Glucose-6-phosphate is oxidized to form ATP, which closes ATP sensitive potassium channels.
- Closure of potassium channels depolarizes the cell membrane, causing voltage gated potassium channels to open.
- When calcium enters the cell causing exocytosis of insulin vesicles.

Insulin receptor:



Insulin receptor

- Insulin receptor is an enzyme linked receptor.
- Consist of four subunits, two Alpha and two Beta held together by disulphide linkages.
- The Alpha subunits lie outside the cell membrane.
- The Beta subunits penetrate the cell membrane, protruding into the cell cytoplasm.
- When insulin binds with Alpha subunits, causing auto-phosphorylation of Beta subunits.
- Auto-phosphorylation of Beta subunits activates tyrosine kinase which causes phosphorylation of intracellular enzymes called insulin receptor substrates.
- The net effect is to activate some of these enzymes while inactivating others.
- In this way insulin produce the desired effects.

Regulation of insulin secretion:

Factors that increase insulin secretion	Factors that decrease insulin secretion
Increased blood glucose	Decreased blood glucose
Increased A.A especially arginine and lysine	Fasting
Increased free fatty acids	Somatostatin
Gastrin, CCK and GIP	Leptin
Glucagon, growth hormone and cortisol	Epinephrine, Nor-epinephrine
Para-sympathetic stimulation (Acetylcholine)	α-adrenergic activity
B-adrenergic stimulation	
Sulfonylurea drugs e.g: Tolbutamide	
GLP-1 and GIP, are called incretins b/c they increase insulin secretion.	

Physiological actions of insulin:

- Insulin promotes metabolism of glucose and its conversion to glycogen in liver and muscle.
- Insulin inactivates liver phosphorylase, activates glucokinase and glycogen synthase.
- Insulin inhibits gluconeogenesis.
- Insulin promotes lipogenesis.
- Insulin inhibits lipolysis by inhibiting hormone sensitive lipase.
- Insulin promotes protein synthesis and decreases protein degradation.
- Insulin and growth hormone interact synergistically to promote growth.
- Insulin promotes potassium uptake into the cells.

Glucagon:

- It is a poly-peptide consists of 29 A.A.
- Secreted by Alpha cells.
- Molecular weight is 3485.
- Hyperglycemic hormone.

Regulation of Glucagon secretion:

Factors that increase Glucagon secretion	Factors that decrease Glucagon secretion
Decreased blood glucose	Increased blood glucose
Increased blood A.A especially alanine and arginine	Insulin
CCK	Somatostatin
Norepinephrine, Epinephrine	Free Fatty acids
Exercise	

Physiological actions of glucagon:

- Increases glycogenolysis.
- Increases gluconeogenesis.
- Increases lipolysis, decreases lipogenesis.
- Increases ketogenesis.
- Increases urea production.

Somatostatin:

- Secreted by Delta cells of islets.
- Polypeptide consists of 14 A.A, same chemical substance as growth hormone inhibitory hormone.
- Half life is 3 minutes.
- Factors that increase somatostatin secretion are increased blood glucose, A.A and fatty acids.

Physiological actions of somatostatin:

- Depresses insulin and Glucagon secretion.
- Decreases motility of stomach, duodenum and gallbladder.
- Decreases secretion and absorption in GIT.

Diabetes Mellitus:

- A metabolic disorder of impaired carbohydrate, fat and protein metabolism.
- Caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin.

Causes of Insulin Resistance

1.	Obesity
2.	Excess glucocorticoids
3.	Excess growth hormone
4.	Pregnancy
5.	Autoantibodies to the insulin receptor
6.	Hemochromatosis

Symptoms of Diabetes Mellitus:

- Polyphagia
- Polydipsia
- Polyuria
- Weight loss
- Hyperglycemia

Types of Diabetes Mellitus:

Type -1 Diabetes	Type-2 Diabetes
Insulin dependent diabetes	Non-insulin dependent diabetes
Caused by lack of insulin secretion	caused by decreased sensitivity of tissues to insulin
90% of β-cells are damaged	No damage to β-cells
Occurs at 14 years of age	occurs after 30 years of age
Also called juvenile onset diabetes	Also called adult onset diabetes
Accounts for 10% of diabetes	Acounts for 90% of diabetes
Body weight is normal	Usually obese
Ketoacidosis, kussmaul breathing	No ketoacidosis
Treatment is insulin administration	Treatment is weight loss, drugs e.g: Metformin, sulfonylureas drugs and insulin

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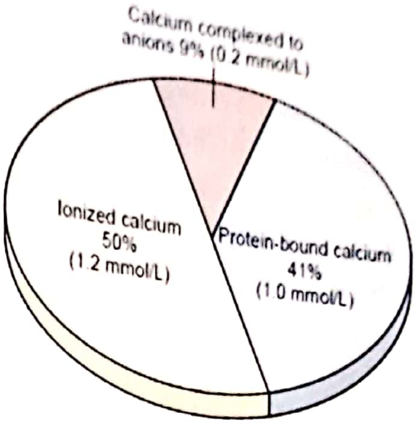
Calcium:

- Normal extracellular calcium concentration is 9-11mg/dl.
- Extracellular calcium is 0.1% of total body calcium.
- Intracellular calcium is 1% of total body calcium.
- Bones contain 99% of total body calcium.



Distribution of Calcium

Plasma calcium:

- 41% is combined with plasma protein.
- 9% is combined with anions.
- 50% is in free form and ionized.

Functions of calcium:

- Controls excitability of nerves and muscles.
- Essential for muscle contraction.
- Regulates permeability of cell membrane.
- Necessary for blood coagulation.
- Formation of bone and teeth.
- Necessary for release of some neurotransmitter from storage vesicles.
- Acts as a second messenger.

Effects of Hypocalcemia:

- Causes nervous system excitement.
- Causes tetany.e.g: laryngospasm and carpopedal spasm.
- Causes seizures.

Effects of Hypercalcemia:

- Depresses nervous system.
- Muscle weakness.
- Decreases QT interval.
- Lack of appetite.
- Constipation.
- Fatigue.

Phosphate:

- The normal plasma phosphate concentration is 3.4 to 4.5 mg /dl.
- Bones contain 85% of body phosphate.
- Intracellular phosphate is 14 to 15% of body phosphate.
- Extracellular phosphate is less than 1% of bo hate.

Functions of phosphate:

- Bone mineralization.
- Participate in energy generation and storage of ATP.
- Component of phospholipids and nucleotides.
- Takes part in cell growth.

Bone:

- Bone is composed of 35% organic matrix and 65% inorganic salts.

Organic matrix:

- 90% collagen fibers.
- 10% ground substance.
- Ground substance is composed of extracellular fluid and proteoglycans.
- Provide tensile strength to bone.

Inorganic salts:

- Composed of combination of calcium and phosphorus salts called hydroxyapatite.
- Its formula is $Ca_{10} (PO4)_6 (OH)_2$.
- Provide compressional strength to the bone.

Mechanism of bone calcification:

- Bone production begins with secretion of collagen molecules and ground substance by osteoblasts.
- The collagen monomers polymerize to form collagen fibers, the resultant tissue becomes osteoid.
- Osteoid is the un-mineralized organic portion of the bone matrix.
- After the osteoid is formed calcium salts begin to precipitate on the surface of collagen fibers to form hydroxyapatite crystals.
- Hydroxyapatite crystallization is regulated by pyrophosphate which inhibits hydroxyapatite crystallization and calcification of bone.
- The level of pyrophosphate is regulated by tissue- nonspecific alkaline phosphatase (TNAP) secreted by the osteoblasts into the osteoid, which breaks down pyrophosphate.
- When pyrophosphate is neutralized, hydroxyapatite crystallization occurs.
- The osteoblast also secretes nucleotide pyrophosphatase phosphodiesterase-1 (NPP-1) and ankylosis protein (ANK), both contribute to pyrophosphate and regulate bone calcification.

Resorption of bone:

- Bone is continually resorbed by osteoclast.
- Osteoclasts are phagocytic, multinucleated, monocytes derivatives cells.
- Parathyroid hormone controls the bone resorptive activity of osteoclasts.

- Osteoclasts do not have parathyroid hormone receptors.
- Parathyroid hormone binds to receptors on osteoblasts stimulating synthesis of receptor activator for nuclear factor K-B ligand (RANKL).
- RANKL binds to receptors RANK on pre-osteoclast cells causing them to differentiate into osteoclasts.
- Osteoblasts also produce osteoprotegerin (OPG) that inhibits bone resorption by blocking RANK and RANKL interaction.

Note:

- Parathyroid hormone and vitamin-D stimulate production of mature osteoclasts through inhibiting OPG production and stimulating RANKL formation.
- Glucocorticoids promote osteoclast activity and bone resorption by increasing RANKL formation and decreasing formation of OPG.
- Estrogen stimulates OPG production and reduces osteoclast activity.

Parathyroid gland:

- Four in number.
- Located behind the thyroid gland.
- 6 mm in length, width is 3 mm and thickness is 2 mm.
- Contains chief cells that secrete PTH.

Parathyroid hormone:

- Secreted by chief cells of parathyroid gland.
- Peptide hormone consists of 84 A.A.
- Molecular weight is 9500.

Physiological actions of PTH:

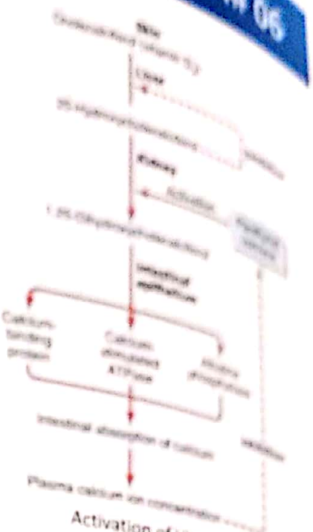
- Stimulates bone resorption and mobilizes calcium and phosphate from bone.
- Increases reabsorption of calcium and decreases phosphate reabsorption by the renal tubules.
- Increases absorption of calcium and phosphate by intestines via activation of vitamin-D.

Regulation of PTH secretion:

- PTH secretion is chiefly controlled by the concentration of free calcium in the plasma.
- Low plasma calcium stimulates PTH secretion.
- High plasma calcium inhibits PTH secretion.

Vitamin-D:

- Fat soluble vitamin.
- Vitamin-D_3 also called cholecalciferol is inactive, formed in the skin as a result of irradiation of 7-Dehydrocholesterol by ultraviolet rays from the sun.
- Cholecalciferol is converted to 25-Hydroxycholecalciferol in the liver, it is less active.
- In the proximal tubules of the kidney 25-Hydroxycholecalciferol is converted to 1, 25-Dihydroxycholecalciferol, it is most active form of vitamin-D. This conversion requires PTH. In the absence of PTH 1, 25-Dihydroxychlecalciferol does not form.


Activation of Vitamin D_3

Physiological Actions of vitamin-D:

- Stimulates bone resorption.
- Increases reabsorption of calcium and phosphate by the renal tubules.
- Increases absorption of calcium and phosphate by the intestines through formation of calbindin.

Calcitonin:

- Secreted by para-follicular cells or C- cells of the thyroid gland.
- Peptide hormone consists of 32 A.A.
- Molecular weight of 3400.

Physiological actions of calcitonin:

- Calcitonin decreases plasma calcium concentration causing its deposition on bone.

Regulation of calcitonin secretion:

- The primary stimulus for calcitonin secretion is increased extracellular calcium and vice versa.

Hypo-parathyroidism:

- Hereditary or as a result of thyroid surgery.
- Causes hypocalcemia.

Primary Hyper-parathyroidism:

- Due to parathyroid tumor.
- Causes hypercalcemia.

Secondary Hyper-parathyroidism:

- Due to vitamin-D deficiency or chronic renal disease.
- Decreased plasma calcium.

Rickets:

- There is decrease in the mineralization of bone.
- Occur in children.
- Occur due to vitamin-D deficiency.
- Bowing of legs may be seen in children.
- Treatment is administration of calcium, phosphate and vitamin-D.

Osteomalacia:

- There is decrease in the mineralization of bone.
- Occur in adults.
- Occur due to vitamin-D deficiency.
- Treatment is administration of vitamin-D.

Osteoporosis:

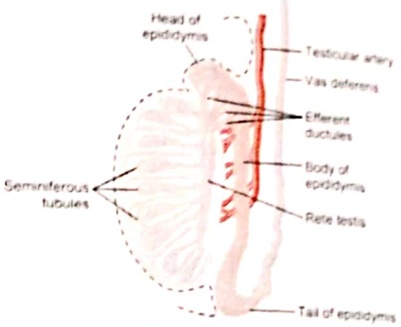
- Bone matrix and mineralization decreases.
- Occur in old age.
- Osteoblast activity decreases and osteoclast activity increases.
- Treatment is administration of bisphosphonates which reduce the activity of osteoclasts.

Male sexual organs:

- Testes are the male sexual organs that play role in reproduction.
- Testes are composed of 900 seminiferous tubules in which spermatogenesis occur.
- The sperm then empty into epididymis, and epididymis leads into vas deferens.
- The vas deferens enlarges into ampulla before it enters the body of prostate gland.
- Seminal vesicles located on each of prostate empty into ampulla.
- The ejaculatory duct is formed by the union of vas deferens and duct of seminal vesicle.
- Prostatic ducts from prostate gland empty into ejaculatory duct.
- The ejaculatory duct opens into the prostatic part of urethra.
- Urethra is connecting testes with exterior.
- Bulbourethral glands located at the origin of urethra, supply the urethra with mucus.

Spermatogenesis:

- It is the process of formation of sperms.
- It occurs in the seminiferous tubules of testes.
- It begins at an average age of 13 years.
- The entire period of spermatogenesis is about 74 days.



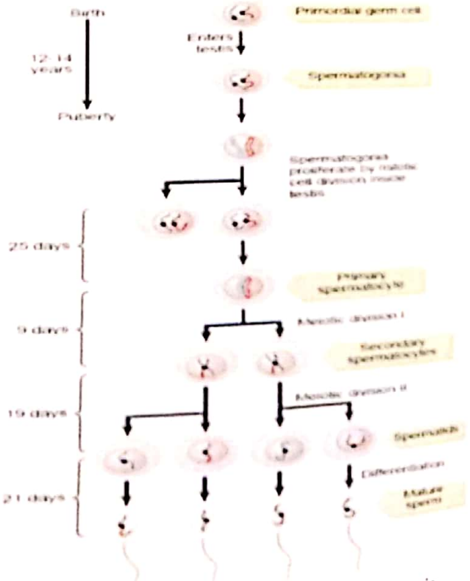
Internal structure of the testis

Steps of spermatogenesis:

- Spermatogonia that cross barrier into sertoli cell layer become modified and enlarged to form primary spermatocytes.
- Primary spermatocytes undergo first meiotic division to form secondary spermatocytes.
- Secondary spermatocytes undergo second meiotic division to form spermatids.

Sex chromosomes:

- In spermatogonium one of the 23 pairs of chromosome carries the genetic information.
- This pair is composed of one X chromosome which is called female chromosome and one Y chromosome which is called male chromosome.
- During meiotic division, the male Y chromosome goes to one spermatid that becomes male sperm, and the female X chromosome goes to another spermatid that becomes a female sperm.
- The sex of the eventual offspring is determined by which one of these two two types of sperm fertilizes the ovum.



Cell division during spermatogenesis

Formation of sperm:

- When spermatids are formed, they are non-motile.
- Spermatids differentiate and elongate to form spermatozoa.
- Each spermatozoan is composed of head, neck, body and tail.
- On the anterior two-thirds of the head is a cap called acrosome, formed from Golgi apparatus.
- The acrosome contains hyaluronidase and proteolytic enzymes that allow the sperm to enter the ovum.
- Movement of the tail provides motility to the sperm.
- Energy is provided by mitochondria in the body of the tail in the form of ATP.
- Using fructose as an energy source.

Maturation of sperm:

- Maturation of sperm occurs in the epididymis.
- When sperm remain in epididymis for 18 to 24 hours, develop capability of motility.

Rate of formation of sperm:

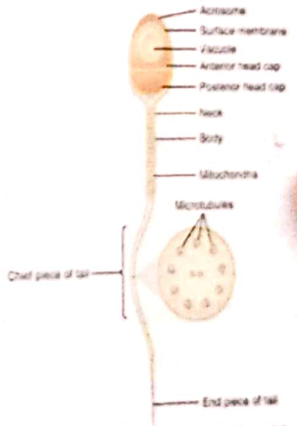
- The two testes formed about 120 million sperm per day.

Storage of sperm:

- Most of the sperm are stored in the epididymis and a small quantity is stored in vas deferens.

Physiology of mature sperm:

- Sperms move through fluid medium at velocities of 1- 4 mm/min.
- The activity of sperm is enhanced in neutral and slightly alkaline medium.
- Acidic medium causes death of sperm.
- The ejaculaled sperm in the female genital tract remains alive for 24 to 48 hours.



Structure of Human spermatozoon

Regulation of spermatogenesis:

- GnRH a hypothalamic hormone act on anterior pituitary to stimulate LH and FSH Secrstion.
- LH stimulates leydig cells to secrete testosterone.
- Testosterone stimulates spermatogenesis.
- Testosterone provides negative feedback for LH secretion.
- FSH stimulates sertoli cells which promote spermiogenesis.
- Sertoli cells secrete inhibin which provides negative feedback for FSH secretion.

formed from testosterone by aromatase enzyme secreted by sertoli cells also promotes spermiogenesis.

Effect of temperature on spermatogenesis:

- Increase in temperature of the testes can prevent spermatogenesis causing degeneration of most cells of the seminiferous tubules.
- Therefor testes are located in the dangling scrotum to maintain temperature of the testes about 2C^0 below the internal temperature.

Seminal vesicles:

- Secrete mucoid material containing fructose, citric acid, prostaglandins and fibrinogen.
- Fructose provide energy to sperm, citric acid also have nutritional value.
- Prostaglandins make female cervical mucus more receptive to sperm movement and cause reverse peristaltic contractions in the uterus and fallopian tubes.
- Fibrinogen form fibrin coagulum that holds the semen in the deeper regions of vagina.

Prostate gland:

- Secretes milky fluid that contains calcium, citrate ion, phosphate ion, clotting enzyme and pro-fibrinolysin.
- Alkaline prostatic fluid neutralizes acidity of seminal fluid and nourishes sperm.

Semen:

- Semen also known as seminal fluid is composed of fluid and sperm ejaculated during male sexual act.
- Seminal vesicles contribute 60% of semen.
- Prostate gland contributes 30% of semen.
- Vas deferens contributes 10% of semen.
- Semen provides transport medium and nourishment to sperm.

Capacitation of sperm:

- *When sperms are ejaculated they are unable to fertilize an oocyte.*
- *Sperms must undergo a period of conditioning called capacitation that last for 1-7 hours.*
- *Capacitation occurs in uterine cavity or uterine tube.*
- *During capacitation glycoprotein and cholesterol are removed from the surface of sperm acrosome.*
- *Capacitated sperms do not show morphologic changes, but they are more active.*
- *Completion of capacitation permits the acrosome reaction to occur.*

One sperm enter the oocyte during fertilization:

- *When first sperm penetrates the zona pellucida of the ovum.*

- Calcium ions diffuse inward through oocyte membrane and cause releasing of cortical granules.
- These granules contain substances that prevent binding of additional sperm.
- Thus only one sperm enter the oocyte during fertilization.

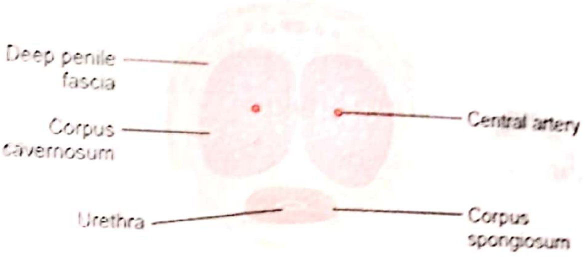
Cryptorchidism:

- Failure of a testis to descend from the abdomen into the scrotum.
- Testosterone secretion by the fetal testes is the stimulus that causes the testes to descend.
- A testis that remains in the abdominal cavity is incapable of forming sperm.
- Cryptorchidism can be treated with human chorionic gonadotropin (hCG).

Stages of the male sexual act:

Erection:

- Erection is the first effect of male sexual stimulation.
- It is caused by parasympathetic impulses.
- The parasympathetic fibers release nitric oxide.
- Nitric oxide activates guanylyl cyclase causing increased formation of CGMP.
- CGMP dilates the arteries of penis and of the erectile tissue.
- As the arteries dilate, blood flow increases.
- This increased blood flow causes ballooning of the erectile tissue, so the penis becomes hard and elongated, this phenomenon is called erection.



Erectile tissue of the penis

Emission:

- Emission is the movement or expulsion of sperm from epididymis, vas deferens, seminal vesicles and prostate gland into internal urethra.
- It is caused by sympathetic impulses.

Ejaculation:

- It is the expulsion of semen from urethra to the exterior.
- It is caused by the rhythmical contraction of the ischiocavernosus and bulbocavernosus muscles that compress the bases of penile erectile tissue.
- It is caused by sympathetic impulses.

Testosterone:

- Secreted by interstitial cells of leydig in the testes.
- Testes secrete large quantities of testosterone in the newborn male infant for the first few months of life and in the adult male after puberty.

- Much of the testosterone is converted into more active hormone Dihydrotestosterone by 5α-reductase in the target tissues.
- After secretion about 97% of testosterone bound with plasma proteins and have half life of 30-60 minutes.
- Testosterone that does not fixed to tissues is converted into andosterone and dehydroepiandrosterone, after secretion they are excreted from the body.

Physiological actions of testosterone:

- Development of penis, scrotum, seminal vesicles and prostate gland.
- Deepening of voice.
- Growth of facial, pubic and axillary hairs.
- Male pattern baldness.
- Increases development of muscle.
- Increases thickness of skin.
- Increases sebaceous glands secretion.
- Stimulates spermatogenesis.

Adiposogenital syndrome:

- Also called frohlich's syndrome or hypothalamic eunuchism.
- Caused by genetic inability of hypothalamus to secrete normal amounts of GnRH.
- This is often associated with abnormality of feeding centre of hypothalamus causing the person to over eat. So obesity occurs along with eunuchism.

Erectile dysfunction:

- An inability of the man to develop an erection.
- Caused by trauma to parasympathetic nerves, neurological disorders and some medications.
- It can be treated with phosphodiesterae-5 inhibitors such as sildenafil (Viagra).
- These drugs increase CGMP levels in erectile tissue by inhibiting the phosphodiesterase enzyme which degrades CGMP.
- So increase in CGMP level causes erection.

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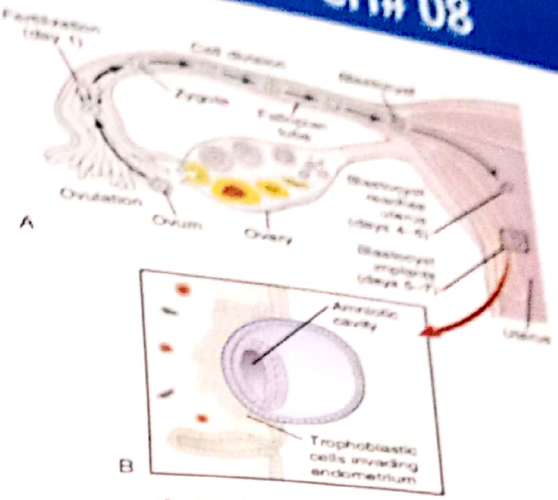
Female reproductive system:

Female reproductive system consist of,

- Ovaries
- Uterine tubes
- Uterus
- Vagina

Oogenesis:

- Oogenesis is the process of formation of mature egg or ovum.
- It occurs in the ovary.


Fertilization (day 1)
Cell division
Zygote
Fallopian tube
Blastocyst
Ovulation
Ovum
Ovary
Blastocyst reaches uterus (days 4-5)
Blastocyst implants (days 5-7)
Uterus
A
Amniotic cavity
Trophoblastic cells invading endometrium
B

Ovulation, Fertilization and Implantation

Steps of oogenesis:

- During fetal development meiosis I begin but arrested in prophase I until puberty.
- After puberty primary oocyte complete meiosis I which gives a secondary oocyte and first polar body that degenerates.
- The secondary oocyte begins meiosis II but arrested in metaphase II.
- The secondary oocyte in metaphase II stage is ovulated.
- After fertilization the secondary oocyte complete meiosis II and gives rise fertilized ovum and a second polar body that degenerates.

Regulation of female sexual cycle:

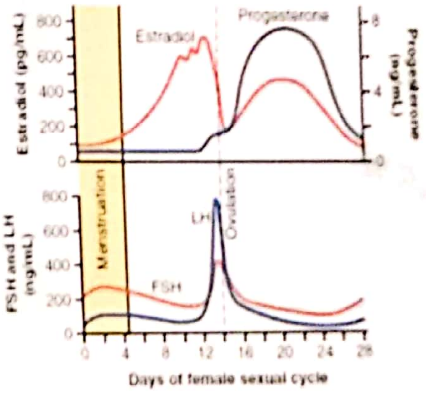
- Hypothalamus secretes GnRH in a pulsatile manner which acts on anterior pituitary to secrete LH and FSH.

FSH:

- Stimulates development of ovarian follicles.

LH:

- Cause ovulation.
- Cause luteinization.
- Stimulate production of estrogen and progesterone by the ovary.



Plasma concentrations of the FSH and LH and Ovarian Hormones

Negative feedback:

- Estrogen and progesterone inhibits FSH and LH secretion.
- Inhibin secreted by granulosa cells of corpus luteum also inhibits FSH and LH secretion.

Positive feedback:

- Estrogen and progesterone stimulate FSH and LH secretion.

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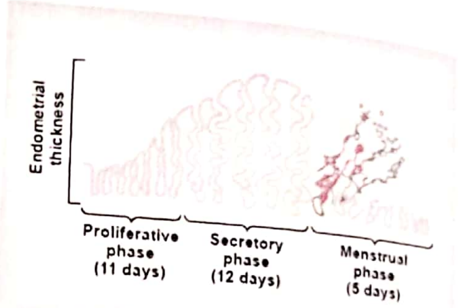
Menstrual cycle:

- It is a monthly cycle in which a series of changes in hormone production and in the structures of the uterus and ovaries of the female occur.
- It begins at an average age of 13 years.
- Average duration of menstrual cycle is 28 days.
- Menarche is the first occurrence of menstrual cycle.
- Menopause is the permanent cessation of menstrual cycle.
- First day of bleeding is called first day of menstrual cycle.

Phases of menstrual cycle:



Phases of Endometrial growth and menstruation during each monthly female sexual cycle.

Follicular phase:

- Also called pre-ovulatory or proliferative phase.
- Estrogen rises.
- The uterine lining builds which has lost during menses.
- Follicles development occurs.

Ovulation:

- Egg is released as a result of LH surge.
- Ovulation always occurs 14 days before the end of the cycle.
- Ovulation day = cycle length - 14
- If the duration of cycle is 28 days ovulation occur at the 14th day of cycle.
- If the duration of cycle is 21 days ovulation occur at the 7th day of cycle.
- LH surge occurs.
- Estrogen reaches its peak.

Luteal phase:

- Progesterone rises.
- Estrogen decreases.
- Uterine lining continuous to build.
- Vascularity and secretory activity of endometrium increases which prepares it for the implantation of fertilized egg.
- Corpus luteum begins to develop which secrete estrogen and progesterone.
- If fertilization does not occur, corpus luteum regresses at the end of the luteal phase. This occurs about at the 26th day of female sexual cycle. As a result estrogen and progesterone level decreases.

Menses:

- Estrogen and progesterone decreases.
- Endometrium sheds.

- About 40 ml of blood and 35 ml of serous fluid are lost.
- Menstrual fluid is non-clotting b/c of presence of fibrinolysin.
- It lasts for 3 -5 days.

Fertile period of menstrual cycle:

- The ovum remains viable for 24 hours after ovulation.
- If fertilization is to take place, sperm must be available soon after ovulation.
- Some sperm can remain fertile in the female reproductive tract for 5 days.
- Thus the fertile period of each sexual cycle is about 4 to 5 days.

Menstrual irregularities:

Amenorrhea:

- Lack of menstrual periods.

Oligomenorrhea:

- Menstruation occurs with intervals of more than 35 days.

Polymenorrhea:

- Menstruation occurs with intervals of less than 21 days.

Menorrhagia:

- Menstrual bleeding lasts for more than 7 days.

Ovarian hormones:

- Ovaries secrete two types of hormones, estrogen and progesterone.
- These hormones are steroids.
- Transported in the blood bound to plasma proteins.
- Have half life of about 30 minutes.

Estrogen:

- There are three major estrogens, estradiol, estrone and estriol.
- The estrogenic potency of estradiol is 12 times that of estrone and 80 times that of estriol.

Physiological actions of estrogen:

- Has both positive and negative feedback effects on FSH and LH secretion.
- Growth of fallopian tubes, uterus and vagina.
- Breast development.
- Growth of pubic and axillary hairs.
- Soft skin and more vascular.
- Inhibits bone resorption and stimulates bone formation.
- Epiphyseal closure.
- Development of secondary sexual characters in females.

- Proliferation of endometrium.
- Thinness of cervical mucus.
- Relax pelvic ligaments of mother which allow easier passage of fetus during childbirth
- Increases uterine contractility.

Physiological actions of progesterone:

- Has both positive and negative feedback effects on FSH and LH secretion.
- Promote secretory changes in the uterine endometrium.
- Breast development.
- Decreases uterine contractility.
- Promote secretion of mucosal lining of fallopian tubes.
- Maintain pregnancy.
- Thickness of cervical mucus.
- Raises body temperayure about 0.5F°.
- Prevent menstruation during pregnancy.
- Development of decidual cells, these are swollen and nutritious cells.
- Increases sensitivity of respiratory center to co_2, so increases respiratory rate.

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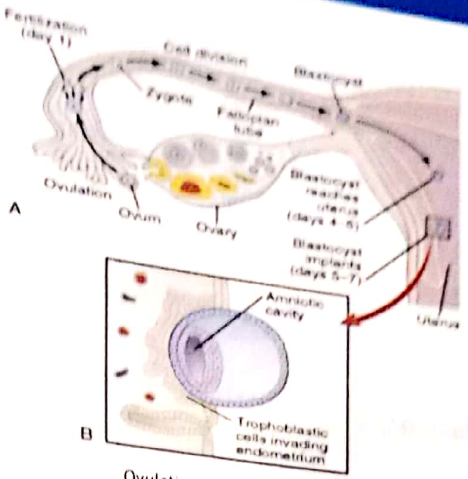
Pregnancy, Parturition and Lactation

CH# 09

Pregnancy:

- Also known as gestation.
- It is the period in which fetus develops inside a female uterus.
- Duration of pregnancy is 9 months or 40 weeks from last menstrual cycle or 38 weeks from fertilization.
- hCG test is used for detection of pregnancy from the second week of pregnancy.
- Pregnancy starts from fertilization until parturition.


Fertilization (day 1)
Cell division
Blastocyst
Zygote
Fallopian tube
Ovulation
Ovum
Ovary
Blastocyst reaches uterus (days 4–5)
Blastocyst implants (days 5–7)
Uterus
A
Amniotic cavity
Trophoblastic cells invading endometrium
B

Ovulation, Fertilization and Implantation

Fertilization:

- It is the fusion of haploid egg and sperm to form diploid zygote.
- Occurs in the ampulla of fallofian tube.
- The zygote divides rapidly and remains in the fallofian tube for 3 days aftrer ovulation.

Sex of the fetus:

- If X chromosome from a sperm combines with X chromosome from an egg, giving an XX combination, child will be female.
- If Y chromosome from a sperm combines with X chromosome from an ovum, giving an XY combination, child will be male.

Implantation:

- It is the attachment of blastocyst to the wall of the uterus.
- Blastocyst reaches uterus on day 4th - 5th after ovulation.
- Implantation of blastocyst occurs on day 5th - 7th after ovulation.
- Implantation results from an action of trophoblast cells that form outer layer of blastocyst.
- Before implantation the blastocyst abtains nutrients from uterine milk.
- During the first week after implantation the embryo obtains nutrients from decidual cells and after first week of implantation from placenta.

Placenta:

- It is the connection b/w uterus and umbilical cord.
- It is feto-maternal organ.
- Fetal part develops from chorion frondosum.
- Maternal part develops from decidua basalis.
- Provides nutrition to embryo after first week of implantation.

Functions of placenta:

- Nutrition
- Respiration
- Excretion of waste products.
- Hormone production.

Hormones in pregnancy:

- During pregnancy placenta forms,
- Human chorionic gonadotropin (hCG)
- Estrogen
- Progesterone
- Human chorionic somatomammotropin

Human chorionic gonadotropin (hCG):

- Secreted by syncytial trophoblast cells.
- Glycoprotein having molecular weight of 39000.
- Secretion begins about 8 - 10 days after ovulation.
- hCG test is used for detection of pregnancy.
- Having same molecular structure and functions as LH.

Functions of hCG:

- Prevents involution of corpus luteum which secretes estrogen and progesterone.
- Prevents shedding of endometrium.
- Acts on testes resulting in production of testosterone.

Human chorionic somatomammotropin:

- Also called human placental lactogen.
- A protein having molecular weight of 22000.
- Secreted from 5th week of pregnancy by placenta.

Functions of human chorionic somatomammotropin:

- Structure and functions similar to those of growth hormone.
- Modifies the metabolic state of the mother during pregnancy.
- Decreases insulin sensitivity and utilization of glucose in mother.
- Promotes release of free fatty acids from maternal fat stores.

Maternal changes during pregnancy:

- Anterior pituitary enlarges and increases corticotropin, thyrotropin and prolactin secret
- Corticosteroid secretion increases.
- Thyroxine secretion increases.
- Parathyroid gland secretion increases.
- The average weight gain during pregnancy is 25-35 pounds.
- Metabolic rate increases.
- Cardiac output and blood volume increases.
- Respiratory rate increases.

Ectopic pregnancy:

- Pregnancy in which implantation takes place outside the uterus.
- Mostly occurs in fallopian tubes.

Preeclampsia:

- It is a pregnancy complication characterized by high blood pressure.
- Usually begins after 20 weeks of pregnancy.
- Kidneys and liver damage also occur.

Eclampsia:

- Extreme degree of preeclampsia.
- Characterized by vascular spasm and clonic seizures, sometimes followed by coma.

Parturition:

1. Baby's head stretches cervix
2. Cervical stretch excites fundic contraction
3. Fundic contraction pushes baby down and stretches cervix some more
4. Cycle repeats over and over again

Theory for the strong construction during labor

- It means birth of the baby.
- Also called childbirth or delivery.
- During pregnancy mostly the uterus undergoes periodic episodes of weak and slow rhythmical contractions called Braxton Hicks contractions.
- The strong contractions that occur during the end of pregnancy that cause parturition are called labor contractions.
- In normal births the head is the first part of the body to be expelled.
- Birth in which buttocks or feet first enter the birth canal is called breech delivery.
- Child birth is a positive feedback mechanism.
- About 350 ml of blood is lost during parturition.
- Lochia is the vaginal discharge after childbirth that last for 8 - 10 days.

Factors that cause parturition:

- Increased ratio of estrogen to progesterone which increase uterine contractility.
- Oxytocin causes contraction of the uterus.
- Fetal membranes release prostaglandins that increase uterine contractions.
- Stretch of the uterine musculature increases their contractility.
- Twins are born on average 19 days earlier than a single child that emphasizes the importance of mechanical stretch in eliciting uterine contractions.
- Stretch of the cervix stimulates the release of oxytocin.

Lactation:

- Lactation is the process by which milk is synthesized and secreted from the mammary glands of female breast after childbirth.

Development of breast:

- Estrogen stimulates growth of the ductal system of the breasts.
- Progesterone is required for full development of the lobules and alveoli.

Factors that promote lactation:

- Prolactin promotes lactation.
- During pregnancy prolactin level increases steadily b/c estrogen stimulates prolactin secretion.
- During pregnancy lactation does not occur b/c estrogen and progesterone block the action of prolactin on the breast, so inhibits lactation.
- After child birth estrogen and progesterone decrease and lactation occurs.
- Lactation is maintained by suckling, which stimulates oxytocin and prolactin secretion.

Prolactin inhibitory hormone:

- The hypothalamus secretes prolactin inhibitory hormone or dopamine that plays an essential role in controlling prolactin secretion.
- The hypothalamus stimulates production of all other anterior pituitary hormones except prolactin that it inhibits.
- Damage to the hypothalamus increases prolactin secretion while depresses secretion of other anterior pituitary hormones.

Milk ejection reflex:

- Also called "Let-down" reflex.
- It is the removing of preformed milk from alveoli into the ducts and out of the nipple.
- Caused by oxytocin.

Ovulation is suppressed in nursing mothers:

- Ovulation does not occur as long as lactation is continuous.
- The reason is that the prolactin inhibits hypothalamic GnRH secretion.
- This inhibition, suppresses anterior pituitary FSH and LH formation. So ovulation does not occur.

Part-VI

GASTROINTESTINAL PHYSIOLOGY

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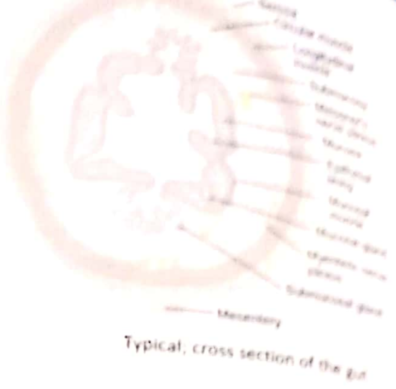
Layers of GIT wall:

- From outward to inward consist of the following layers.



Typical; cross section of the gut

Serosa:

- Thin layer of connective tissue.

Muscularis :

- Muscular layer.
- Outer longitutinal and inner circular smooth muscle layer.
  - Has Myenteric nerve plexus b/w longitudinal and circular muscle layers.

Submucosa:

- Layer of connective tissue.
- Has Meissner's plexus.

Mucosa:

Consist of,

- Epithelial lining
- Lamina propria
- Muscularis mucosa

GI smooth muscle function as a syncytium

- Smooth muscle fibers are arranged in bundles.
- These bundles are present in longitudinal and circular muscle layers.
- Fibers in each bundle are electrically connected by gap junctions.
- When an action potential is elicited anywhere within the muscle, it travels in all directions in the muscle.
- So GI muscle act as a syncytium.

Electrical activity of GI smooth muscle

- The smooth muscle of the GIT is excited by continual slow, intrinsic electrical activity along the membranes of the muscle fibers. This activity has two types of electrical waves.

Slow waves

- Not action potential.
- Slow undulating changes in resting membrane potential.
- Intensity varies b/w 5-15 mv.

- Frequency ranges b/w 3-12 per minute in different parts of GIT.

I. About 3 in the body of stomach.
II. 8 or 9 in terminal ileum.
III. 12 in the duodenum.

- Rhythmicity of GI contraction is determined by the frequency of slow waves.
- Frequency of slow waves = rhythmicity of GI contraction.
- Generated by the interaction of interstitial cells of Cajal.
- Interstitial cells of Cajal are electrical pacemakers for smooth muscle cells.
- Do not cause muscle contraction except in the stomach.
- Control appearance of intermittent spike potentials.

Spike potentials:

- Action potentials.
- Generated when RMP becomes more positive than -40 mv.
- Greater the rise in RMP, greater will be the frequency of spike potentials.
- Frequency ranges b/w 1-10 spikes per second.
- Lasts as long as 10 -20 milliseconds.
- Generated by the entry of calcium ions.

Resting membrane potential of GI smooth muscle:

- The RMP of GI smooth muscle fibers is b/w -50 and -60 mv.

Depolarization of GI smooth muscle:

- When RMP becomes less negative depolarization of the membrane occurs.
- Muscle fibers become more excitable.

Factors causing depolarization:

- Stretch of the muscle.
- Acetylcholine.
- Parasympathetic nerves.

Hyperpolarization of GI smooth muscle:

- When RMP becomes more negative hyperpolarization of the membranes occurs.
- Muscle fibers become less excitable.

Factors causing hyperpolarization:

- Epinephrine and norepinephrine.
- Sympathetic nerves stimulation.

Mechanism of smooth muscle contraction:

- Entry of calcium ions causes smooth muscle contraction.

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- Calcium ions acting through a Calmodulin control mechanism.
- Activate the myosin filaments in the fiber.
- Attractive forces develop b/w the myosin filaments and the actin filaments.
- Causing smooth muscle contraction.

Enteric nervous system:

- Provides intrinsic innervation to the GIT.
- Located in the wall of GIT, beginning in esophagus and extending to the anus.
- Composed of 100 million neurons.
- Control movement and secretion in GIT.
- Composed of myenteric plexus and submucosal plexus.
- Function independently of sympathetic and parasympathetic extrinsic fibers.

Myenteric plexus:

- Also called auerbach's plexus.
- Located b/w longitudinal and circular muscle layers.
- Consist of linear chain of interconnecting neurons.
- Outer plexus.
- Controls gastrointestinal movements.
- Mainly excitatory, some neurons are inhibitory.

Submucosal plexus:

- Also called meissner's plexus.
- Located in the submucosa.
- Inner plexus.
- Control GI secretion and local blood flow.

Autonomic control of GIT:

- Composed of parasympathetic and sympathetic innervation.

Parasympathetic innervation:

- Made up of cranial and sacral divisions.
- Cranial parasympathetic by way of vagus nerve innervates stomach, pancreas and first half of the large intestine.
- The sacral parasympathetic by way of pelvic nerves innervates the distal half of the large intestine.

Functions:

- Increases activity of the enteric nervous system.
- Increases GIT motility.
- Causes sphincter relaxation.

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- Increases GIT secretions.

Sympathetic innervation:

- Originate in the spinal cord b/w segments T5 and L2.
- Innervate all of the GIT.

Functions:

- Decreases GIT motility.
- Causes sphincter relaxation.
- Decreases GIT secretion.
- Decreases activity of the enteric nervous system.

Gastrointestinal reflexes:

- There are three types of gastrointestinal reflexes.

Reflexes that occur entirely within the enteric nervous system.

e.g: Reflexes of gastrointestinal secretion and peristalsis.

Reflexes from the gut to the sympathetic ganglia and then back to the gut.

e.g: Gastrocolic reflex, enterogastric reflexes and colonoileal reflex.

Reflexes from the gut to the spinal cord or brainstem and then back to the gut.

e.g: Pain reflexes and defecation reflexes.

Hormonal control of GI motility:

- The GI hormones are released into the portal circulation and exert physiological actions on target cells.

Gastrin:

- Gastrin is a peptide hormone composed large of 34 A.A and little gastrin of 17 A.A.
- Secreted by G cells of stomach and duodenum.

Stimuli for secretion:

- Protein and peptide in the stomach.
- Stomach distention.
- Vagal stimulation.
- Acid inhibits its secretion.

Actions:

- Stimulates gastric mucosal growth.

Cholecystokini or CCK:

- It is a peptide hormone composed of 33 amino acids.
- Secreted by I cells of duodenum, jejunum and ileum.

Stimuli for secretion:

- Protein
- Fat
- Acid

Actions:

- Stimulates pancreatic enzymes secretion.
- Stimulates pancreatic bicarbonate secretion.
- Stimulates gallbladder contraction and causes relaxation of the sphincter of oddi for secretion of bile.
- Stimulates growth of exocrine pancreas.
- Inhibits gastric emptying.
- Inhibits appetite so play role in satiety.
- Decreases gastric emptying.

Secretin:

- It is a peptide hormone composed of 27 A.A.
- Secreted by S cells of the duodenum.
- First hormone to be discovered.

Stimuli for secretion:

- Acid
- Fat

Actions:

- Stimulates pancreatic bicarbonate secretion.
- Stimulates biliary bicarbonate secretion.
- Stimulates growth of exocrine pancreas.
- Inhibits gastric acid secretion.

Gastric inhibitory peptide:

- It is a peptide hormone composed of 42 A.A.
- Secreted by K cells of the duodenum and jejunum.

Stimuli for secretion:

- Protein
- Fat
- Carbohydrate

Actions:

- Stimulates insulin release.
- Inhibits gastric acid secretion.

Motilin:

- It is a peptide hormone composed of 22 A.A.
- Secreted by M cells of the duodenum and jejunum.

Stimuli for secretion:

- Fat
- Acid
- Fasting

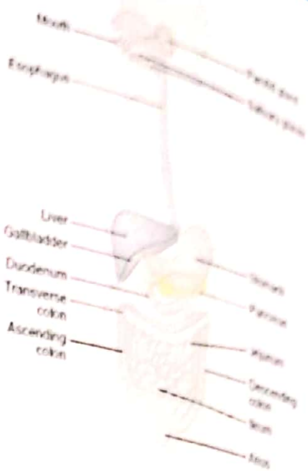
Actions:

- Stimulates gastric motility.
- Stimulates intestinal motility.

- ➢ It is the process of taking food into the body.

Mastication:

- ➢ It is the process by which ingested food is crushed into small pieces mixed with saliva and formed into bolus in preparation for swallowing.
- ➢ Increases the surface area of food for enzyme activity.
- ➢ Prevent irritation of the GI system by large food particles.



Alimentary tract

Swallowing:

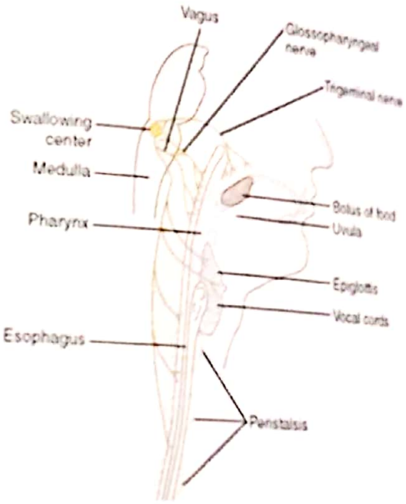
- ➢ It is the process by which food moves from mouth into the stomach.

Swallowing phases:

- ➢ There are three phases,

Oral phase:

- ➢ Voluntary phase.
- ➢ Initiates the swallowing process.
- ➢ Tongue plays a vital role in this phase, b/c it elevates and propels bolus into pharynx.
- ➢ Bolus moves from oral cavity into the oropharynx.



Swallowing mechanism

Pharyngeal phase:

- ➢ Involuntary phase.
- ➢ Bolus moves from the oropharynx into the esophagus.
- ➢ Shortest phase.
- ➢ Nasopharynx is closed.
- ➢ Respiration stops.
- ➢ Upper esophageal sphincter opens.

Esophageal phase:

- Involuntary phase.
- Bolus moves through the esophagus into the stomach by peristalsis.
- Lower esophageal sphincter relaxes.
- Time duration is 5 to 8 seconds.

Functions of the stomach:

- Storage of food.
- Mixing of food with gastric secretion.
- Digestion of food.
- Food in the stomach is converted into chyme.

Hunger pangs:

When the stomach is empty for many hours, the stomach undergoes intense rhythmic contraction called hunger contraction.

When hunger contraction occur the person experience pain in the stomach called hunger pangs.

Hunger pangs can begin after 12 – 24 hours of last food ingestion.

Stomach Emptying:

It is the process by which the contents of the stomach are moved into the duodenum.

Factors that cause stomach emptying:

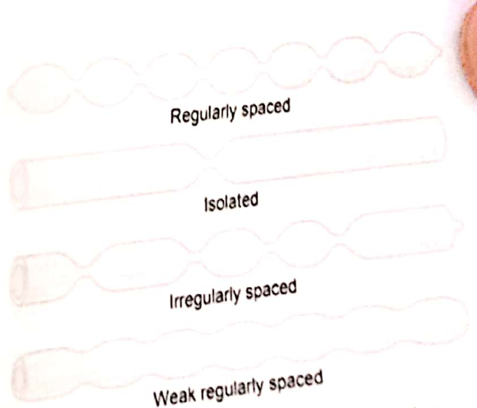
- Peristaltic waves.
- Systolic contractions of the antrum.
- Reduction in the size of the stomach.

Regulation of stomach emptying:

- Stretching of the stomach wall in response to increased food volume promotes stomach emptying.
- Gastrin promotes stomach emptying.
- Fat in the duodenum inhibits gastric emptying by release of CCK.
- Acidity of the duodenal chyme inhibits gastric emptying.

mall intestine Motility:

- Two types of motility occur,



Segmentation movement of the small intestine

Segmentation contraction:

- Caused by distention of intestinal wall.
- Consist of oscillating, ring like contractions of circular smooth muscle.
- Contractile ring occur at every few centimeter, dividing the small intestine into segments.
- B/w the contracted segments are relaxed area containing chyme.
- Churn and mix chyme with secretions of the small intestine.
- Help propel the chyme down the intestine.

Peristaltic contractions:

- Wave of contraction preceded by wave of relaxation.
- Highly coordinated, contraction behind the bolus and relaxation in front of the bolus.
- Move at a velocity of 0.5 - 2 cm /sec.
- Faster in the proximal intestine and slower in the terminal intestine.
- Causes propagation of chyme.

Factors affecting intestinal peristalsis:

- Gastrin, CCK, insulin, motilin and serotonin enhance intestinal motility.
- Secretin and glucagon inhibit small intestinal motility.

Peristaltic Rush:

- Powerful and rapid peristaltic contractions.
- Caused by intense irritation of the intestinal mucosa.
- Partly initiated by extrinsic nervous reflex and partly by myenteric reflex.
- Sweeping the contents of the intestine into the colon and thereby relieving the small intestine of irritative chyme or excessive distention.
- Results in diarrhea.

Ileocecal valve:

- It is a sphincter muscle situated at the junction of the ileum and the colon.
- Allow digested food to pass from small intestine into colon and prevents back flow.
- Pressure and chemical irritation in the ileum relax sphincter and excite peristalsis in ileum.
- Pressure and chemical irritation in the ileum inhibits peristalsis of ileum and sphincter is contract.

Colon Motility:

- Two types of movements occur,

Mixing movements:

- Also called Haustrations.
- Ring like constrictions occur.
- At each constriction about 2.5 cm of the circular muscle contract.
- Tenia coli which are aggregation of longitudinal muscle of the colon also contract.
- These contractions cause the unstimulated portion of the colon to bulge outward into b like sacs called haustrations.
- Helps in mixing and propulsion of food.

Mass movement:

- Propulsive movements.
- Occur 1-3 times a day.

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- Initiated by gastrocolic and duodenocolic reflexes.
- Propels the chyme into rectum.

Defecation reflex:

When feces moves into the rectum.

- The rectum is distended which activates stretch receptors.
- The stretch receptors signal sacral spinal cord.
- Parasympathetic nerves from sacral spinal cord contract muscles of rectum.
- Internal anal sphincter is relaxed.
- External anal sphincter is voluntarily controlled.
- If the conditions are right, voluntarily relaxation of external anal sphincter allows defecation. Otherwise the reflex subsides until the rectum is filled again.

Saliva:

- Mixture of water and electrolytes secreted by salivary glands.

Secretion of saliva:

- Saliva is secreted by parotid, submandibular and sublingual glands.
- Parotid glands secrete serous secretion.
- Submandibular and sublingual glands secrete both serous and mucus secretion.
- Saliva is secreted 1000 ml per day.
- Saliva has a PH 6 - 7.

Composition of saliva:

- water
- Mucus, a glycoprotein.
- High concentration of potassium and bicarbonate ions.
- Low concentration of sodium and chloride ions.
- α-amylase, lingual lipase, kallikrein and lysozymes.

Mechanism of saliva formation:

- It occurs in two steps.

First step:

- Occurs in acinar cells.
- Acini secrete primary saliva with a composition similar to plasma (isotonic fluid).

Second step:

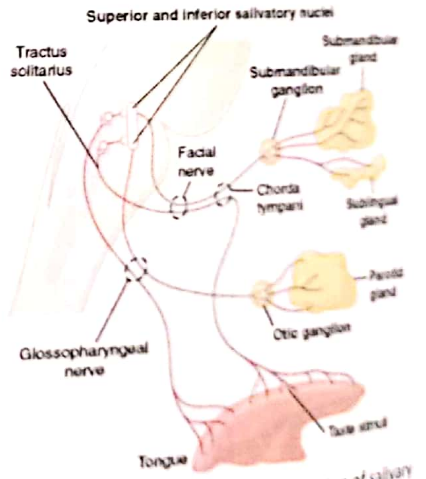
- Occurs in salivary ducts.
- Potassium ions are secreted into ducts in exchange for sodium ions reabsorption from ducts.
- Bicarbonate ions are secreted into ducts in exchange for chloride ions reabsorption from ducts.
- Saliva becomes hypotonic b/c ducts are relatively impermeable to water.

Regulation of salivary secretion:

- Both parasympathetic and sympathetic supply increase salivary secretion.

Parasympathetic supply:

- From superior and inferior salivatory nuclei.
- Produces a large volume of watery saliva rich in enzymes.



Parasympathetic nervous regulation of salivary secretion

Sympathetic supply:

- From superior cervical sympathetic ganglion.
- Produces a small, thick secretion of saliva rich in enzymes.

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Functions of saliva:

- Lubrication
- Starch digestion
- Cleansing and protection
- Appreciation of taste

Gastric secretion:

- There are different types of cells in the stomach which contribute in gastric secretion.

Parietal cells:

- Secrete HCl
- Secrete intrinsic factor
- Intrinsic factor is essential for the absorption of vitamin B_{12} in ileum.
- Intrinsic factor deficiency causes pernicious anemia.

Chief cells:

- Secrete pepsinogen which is inactive.
- Pepsinogen is converted into its active form pepsin by HCl.
- Pepsin acts as proteolytic enzyme.
- Pepsin has molecular weight of 35000.
- Its secretion is stimulated by acetylcholine.

G cells:

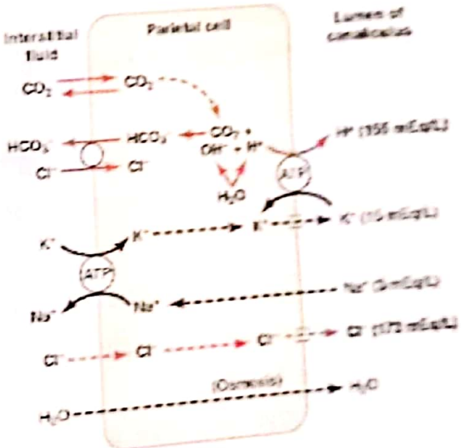
- Secrete gastrin.

Mucous neck cells:

- Secrete mucous.

Enterochromaffin like cells:

- ECL cells secrete histamine.



Mechanism of HCL Secretion

Mechanism of HCl secretion:

- Parietal cells secrete HCl.
- In the parietal cells carbon dioxide and water are converted to carbonic acid catalyzed by carbonic anhydrase.
- Carbonic acid dissociates to form hydrogen ion and bicarbonate ion.
- Hydrogen ion is secreted into the lumen of canaliculi of parietal cells in exchange for potassium ion by hydrogen potassium ATPase.
- Bicarbonate ion is pumped outside parietal cell in exchange for chloride ion into parietal cell at basolateral membrane.

Chloride ion moves out of parietal cell through chloride channels into lumen of canalicu giving strong solution of HCl.

Factors that stimulate gastric acid secretion:

- ➢ Acetylcholine
- ➢ Gastrin
- ➢ Histamine

Factors that inhibit gastric acid secretion:

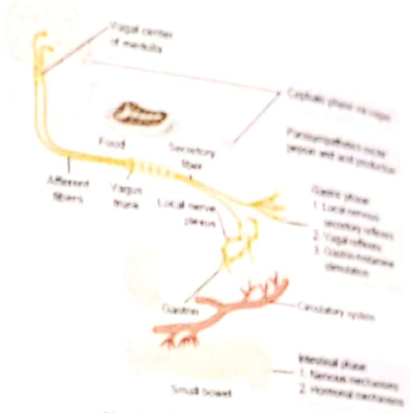
- ➢ Low PH inhibits gastrin secretion, so inhibits acid secretion.
- ➢ Somatostatin
- ➢ prostaglandins
- ➢ Gastric inhibitory peptide
- ➢ Vasoactive intestinal polypeptide.

Drugs that block gastric acid secretion:

- ➢ Atropine a cholinergic antagonist.
- ➢ Omeprazole a proton pump inhibitor.
- ➢ Cimetidine a H_2 receptor antagonist.

Phases of gastric secretion:

- ➢ Total gastric secretion is 1500 ml day.
- ➢ PH of gastric secretion is 1- 3.5.
- ➢ Gastric secretion occur in three phases,



Phases of gastric secretion and their regulation

Cephalic phase:

- ➢ Gastric secretion occurs before food enters the stomach.
- ➢ Results from the sight, smell, thought or taste of food via vagus nerve.
- ➢ Accounts for 30% of gastric secretion.

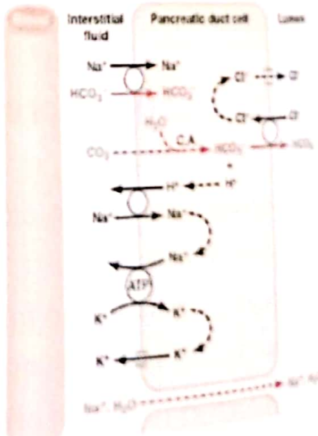
Gastric phase:

- ➢ Gastric secretion occurs when food enters the stomach.
- ➢ Results from vasovagal reflexes, local enteric reflexes and response to gastrin.
- ➢ Accounts for 60% of gastric secretion.

Intestinal phase:

- ➢ Gastric secretion occurs when food is in duodenum.
- ➢ Results from nervous reflexes and intestinal gastrin.
- ➢ Accounts for 10% of gastric secretion.

Pancreatic secretion:



Mechanism of Pancreatic secretion

- ➢ Pancreas is elongated gland lies behind and below the stomach.
- ➢ Pancreas has acini and ducts.

- Pancreatic acinar cells secrete digestive enzymes.
- Pancreatic ductules and ducts secrete sodium bicarbonate solution.
- pH is 8 – 8.3.
- Isotonic
- Secretion is 1000 ml/day.

Pancreatic digestive enzymes:

Protein digestive enzymes:

Trypsinogen:

- Inactive.
- Converted into active form trypsin by enterokinase secreted by lining of small intestine.

Chymotrypsinogen:

- Inactive.
- Converted into active form chymotrypsin by trypsin.

Procarboxypeptidase:

- Inactive.
- Converted into active form carboxypeptidase by trypsin.

Carbohydrate digestive enzymes:

Pancreatic amylase:

- Secreted in active form.
- Hydrolyze starches and glycogen.
- Cannot hydrolyze cellulose.

Fat digestive enzymes:

Pancreatic lipase:

- Secreted in active form.
- Becomes efficient in the presence of colipase.
- Hydrolyze triglycerides into fatty acids and Monoglycerides.

Cholesterol esterase:

- Hydrolyze cholesterol esters into cholesterol and fatty acids.

Phospholipase:

- Splits fatty acids from phospholipids.

Mechanism of secretion of Bicarbonate ions:

- Water and carbon dioxide combine under the influence of carbonic anhydrase to form carbonic acid.
- Carbonic acid dissociates to form hydrogen and bicarbonate ions.
- The hydrogen ions are exchanged for sodium ions through basolateral membrane of cells.
- The sodium ions are removed by the sodium potassium ATPase.
- The bicarbonate ions are exchanged for chloride ions through the luminal membrane of the cell into the lumen of the duct.
- Sodium ions and water follow the bicarbonate ions into the duct.

Composition of pancreatic secretion:

- Isotonic.
- water
- Same sodium and potassium ions concentrations as plasma.
- Higher bicarbonate ions concentration than plasma.
- Lower chloride ions concentration than plasma.
- Pancreatic digestive enzymes.

Factors that stimulate pancreatic secretion:

- Acetylcholine
- CCK Stimulate secretion of pancreatic enzymes and bicarbonate solution.
- Secretin stimulates secretion of bicarbonate solution.

Functions of pancreatic secretion:

- Digest protein, carbohydrates and fats.
- Highly alkaline, neutralizes HCl in the chyme that enters duodenum.

Bile secretion by the liver:

- Secreted 1000 ml/day.
- PH of bile is 7.8.

Composition of bile:

- Water
- Bile salts
- Bilirubin
- Cholesterol, lecithin and fatty acids.
- Sodium, potassium, calcium, chloride and bicarbonate ions.
- No enzyme.

Formation of bile:

- Cholic acid and chenodeoxycholic acid are synthesized by hepatocytes from cholesterol.

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- These bile acids are conjugated with glycine or taurine to form their respective bile salts.
- These bile salts are then secreted in the bile.
- Electrolytes and water are added to the bile.

Storage of bile:

- Bile is secreted continuously by liver and is stored in the gallbladder.
- Capacity of gallbladder for bile storage is 30 - 50 ml.

Concentration of bile:

- Bile is concentrated in the gallbladder by the reabsorption of water and electrolytes except calcium by the gallbladder mucosa.

Regulation of bile secretion:

- CCK causes contraction of the gallbladder and relaxation of the sphincter of oddi.
- Secretin stimulates biliary bicarbonate secretion.
- Acetylcholine causes contraction of the gallbladder.

Functions of bile:

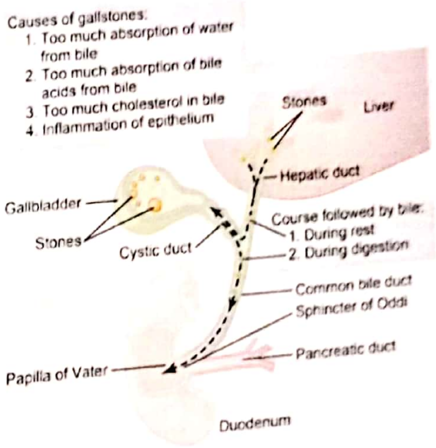
- Fat digestion.
- Neutralizes gastric acid in the small intestine.
- Excretion of bilirubin.

Gallstones:

- Gallstones are pieces of solid material that form in the gallbladder.

Causes of gallstone:

- Too much absorption of water from bile.
- Too much absorption of bile acids from bile.
- Too much cholesterol in the bile.
- Inflammation of gallbladder epithelium.



Formation of gallstones

Bilirubin:

- Greenish yellow bile pigment.
- Major end product of hemoglobin degradation.
- Normal plasma concentration of bilirubin is 0.5 mg/dl.
- Conjugated in liver with glucuronic acid and sulfate and transported into intestine.
- In intestine bilirubin is converted by bacterial action into highly soluble substance urobilinogen.
- Some urobilinogen is excreted by the kidneys into urine.
- After exposure to air in the urine, urobilinogen becomes oxidized to urobilin.

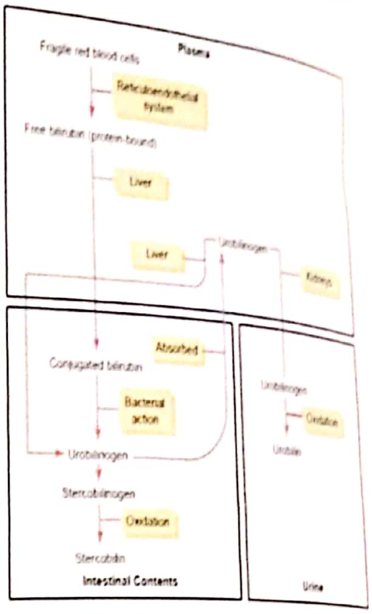
it becomes oxidized to stercobilin.

Jaundice:

- Body tissues become yellow coloured.
- Excess bilirubin in the extracellular fluid.
- Van den Bergh test is used to measure bilirubin level in the blood.
- In severe cases bilirubin deposits in the brain producing neurological disturbances called kernicterus.

Causes of jaundice:

- Excessive breakdown of red blood cells.
- Obstruction of the bile ducts or damage to the liver cells.



Bilirubin formation and excretion

Types of jaundice:

- There are two types of jaundice.
- Van den Bergh reaction can differentiate b/w them.

Hemolytic jaundice:

- Excessive production of bilirubin occurs.
- Caused by excessive breakdown of red blood cells.
- Excretory function of liver is normal.
- Bilirubin is in unconjugated form.
- Van den Bergh reaction is indirect positive.

Obstructive jaundice:

- Bilirubin production is normal.
- Caused by obstruction of the bile ducts or damage to the hepatic cells.
- Bilirubin formed cannot pass from the blood into the intestine.
- Bilirubin is in conjugated form.
- Van den Bergh reaction is direct positive.

Secretions of the small intestine:

- Its secretion is 1800 ml/day.
- PH is 7.5 - 8.
- Brunner,s glands secrete alkaline mucus.
- Goblet cells secrete mucus.
- Enterocytes secrete water and electrolytes.

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Digestive enzymes in the small intestinal secretion:

Epithelial cells lining intestinal mucosa secrete,

- peptidases
- sucrase, maltase, isomaltase and lactase.
- Intestinal lipase
- Enterokinase

Composition of small intestinal secretion:

- Water
- Mucus
- Sodium, potassium, chloride and bicarbonate ions.
- Digestive enzymes

Regulation of small intestine secretion:

- The most effective stimuli for small intestine secretion are local stimulation of the intestinal mucous membrane.

Functions of small intestine secretion:

- Provides protection to intestinal wall.
- Digestion

Secretion of large intestine:

- Large intestine secretes only mucus.

Regulation of mucus secretion:

- Direct, tactile stimulation of the epithelial cells lining the intestine.
- Local nervous reflexes to mucus cells.
- Parasympathetic stimulation.

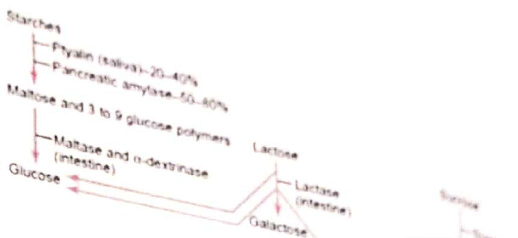
Functions of mucus:

- Provides protection to intestinal wall.
- Hold fecal matter together.

Digestion of carbohydrates:

Digestion of carbohydrates in the mouth:

- Digestion of carbohydrates begins in the mouth by ptyalin or alpha amylase secreted by parotid glands.
- Hydrolyzes starch into maltose and other polymers containing 3 to 9 glucose molecules.



Digestion of carbohydrates

Digestion of carbohydrates in the stomach:

- Acidic environment of the stomach blocks the activity of alpha amylase, so there is no carbohydrate digestion.

Digestion of carbohydrates by the pancreatic amylase:

- Hydrolyzes starch into maltose and small polymers containing 3 to 9 glucose molecules.

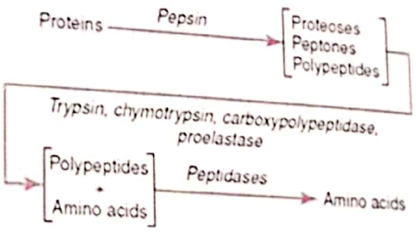
Digestion of carbohydrates by intestinal enzymes:

- Maltase splits maltose into two glucose molecules.
- Lactase splits lactose into galactose and glucose molecules.
- Sucrase splits sucrose into fructose and glucose molecules.
- Alpha dextrinase splits small polymers of glucose into multiple molecules of glucose.

Digestion of proteins:

Digestion of proteins in the stomach:

- Pepsin initiates protein digestion.
- Convert protein to proteoses, peptones and polypeptides.



Digestion of proteins

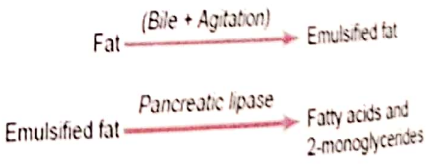
Digestion of protein by pancreatic proteolytic enzymes:

- Trypsin, chymotrypsin, carboxypeptidase and elastase split partial breakdown products of protein into small polypeptides and A.A.

Digestion of small protein molecules by peptidases of small intestine:

- Peptidases split polypeptides into tripeptides, dipeptides and into A.A.

Digestion of Fats:



Digestion of Fats

Digestion of fats in the stomach:

- Small amount of triglycerides is digested in the stomach by lingual lipase.
- Lingual lipase is secreted by Ebner,s glands on dorsal surface of tongue.

Emulsification of fat by bile acids and lecithin:

- Bile salts and lecithin are powerful emulsifying agents.
- They emulsify fat into small droplets, increasing surface area for digestion.

Digestion of fat by pancreatic enzymes:

- Pancreatic lipase hydrolyzes triglycerides into fatty acids and monoglycerides.
- Cholesterol esterase hydrolyzes cholesterol esters into cholesterol and fatty acids.
- Phospholipase splits fatty acids from phospholipids.

Digestion of triglycerides by intestinal lipase:

- Intestinal lipase hydrolyzes triglycerides into fatty acids and monoglycerides.

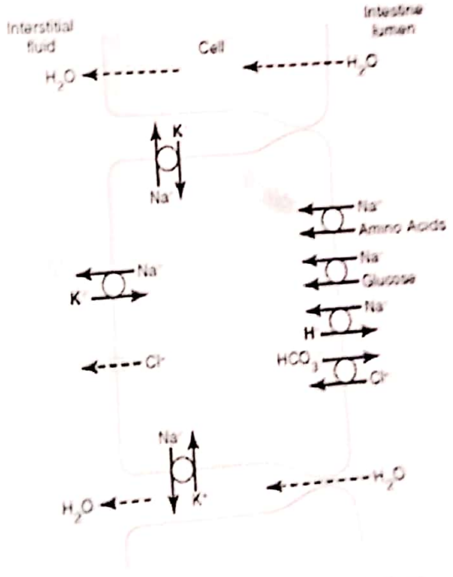
Absorption in the small intestine:

Absorption of carbohydrates:

- Glucose and galactose are absorbed by sodium glucose linked transporter -1 (SGLT-1) in the luminal membrane. (secondary active transport linked to sodium)
- Fructose is absorbed by facilitated diffusion in the luminal membrane.

Absorption of proteins:

- Amino acids are absorbed by secondary active transport linked to sodium in the luminal membrane.
- Dipeptides and tripeptides are absorbed by hydrogen dependent co-transporters in the luminal membrane.



Absorption though intestinal epithelium

Absorption of lipids:

- Micelles bring the products of fat digestion to the brush border of the intestine.
- Then products of fat digestion fatty acids, monoglycerides and cholesterol diffuse across the luminal membrane into the cells.
- In the intestinal cells triglycerides is resynthesized and forms chylomicrons.
- Chylomicrons leave intestinal cells and enter blood stream via lymphatic circulation.

Absorption of water and electrolytes:

- Water, sodium, potassium and chloride absorption occur in small intestine.
- Calcium and iron absorption also takes place.

Absorption in large intestine:

- The following substances are absorbed in large intestine,
- water
- sodium and chloride ions
- bile salts
- Vitamin K and vitamin B.

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Disorders of swallowing and the Esophagus:

Dysphagia:

- It is a medical condition in which there is difficulty in swallowing.

Achalasia:

- It is a condition in which the lower esophageal sphincter fails to relax during swallowing.
- Food swallowed into the esophagus fails to pass from esophagus into the stomach.
- In severe cases esophagus enlarged, this condition is called megaesophagus.

Causes:

- Damage in the neural network of the myenteric plexus in the lower two –thirds of the esophagus.

Gastro-Esophageal reflux disease or GERD:

- It is a condition in which the lower esophageal sphincter becomes weakened and the acidic food from the stomach reflux into the esophagus.
- There is esophageal burning and heartburn.

Barrett's esophagus:

- In severe cases of GERD the epithelial lining of esophagus change from squamous epithelium to columnar epithelium due to stress of acidic reflux.
- These metaplastic cells are better able to handle the new stress.

Disorders of the stomach:

Gastritis:

- It is an inflammation of the gastric mucosa.

Achlorhydria:

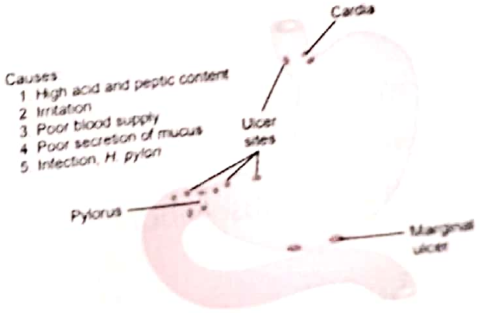
- It is a condition in which the stomach fails to secrete Hcl.

Pernicious anemia:

- It is a type of anemia that results from vitamin b12 deficiency.
- There is impaired uptake of vitamin b12 due to absence of intrinsic factor.

Peptic Ulcer:

- It is an excoriated area of the stomach or duodenal mucosal lining.
- It occurs frequently along the lesser curvature at the antral end of the stomach.



Peptic Ulcer

Causes:

- High acid content.
- Poor secretion of mucus.
- H- pylori infection.
- H-pylori release ammonium that liquefies the barrier and stimulates secretion of hcl.

Treatment:

- Antibiotics such as amoxicillin and clarithromycin to eradicate h-pylori.
- Omeprazole and cimetidine to inhibit acid production.
- Antacids such as magnesium hydroxide to neutralize gastric acid.
- Mucosal protective agents such as sucralfate and bismuth.

Zollinger - Ellison disease:

- Stomach produces too much acid.
- Results in peptic ulcer.
- Caused by a pancreatic tumor that secretes gastrin.
- Too much gastrin results in over production of gastric acid by parietal cells.

Disorders of the small intestine:

Pancreatitis:

- It is an inflammation of the pancreas.
- Occurs when pancreatic proteolytic enzymes start digestion of the pancreas.

Causes of pancreatitis:

- Drinking excess alcohol.
- Blockage of the papilla of vater by a gallstone.

Cystic fibrosis:

- It is a disease of pancreatic secretion.
- Results from a defect in chloride channels.
- Caused by a mutation in cystic fibrosis trans-membrane conductance regulator gene
- There is deficiency of pancreatic enzymes.
- Results in malabsorption and steatorrhea.

Sprue:

- It is an autoimmune disease that damages the lining of the small intestine.
- Damage is due to a reaction to eating gluten, a protein present in wheat and rye.
- Results in malabsorption by the small intestinal mucosa.

Steatorrhea:

- It is a condition in which there is excess fat in the stools.
- Stools may be bulky and difficult to flush.
- Stools have a pale and oily appearance.
- Stools can be of foul smelling.

Causes of steatorrhea:

- Lack of pancreatic lipase.
- Lack Of bile salts.
- Sprue or celiac disease.
- Cystic fibrosis.

Disorders of the large intestine:

Constipation:

- It is a condition in which bowel movements become less frequent and stools become difficult to pass, associated with large quantities of dry and hard stools in colon.

Causes:

- Decreased fluid intake.
- Inappropriate bowel habits.
- Immobility.

Treatment:

- Laxatives are drugs that facilitate evacuation of stools from the bowel.

Diarrhea:

- It is characterized by loose, watery stools occur more than three times a day.
- In diarrhea there is loss of isotonic fluid.

Causes:

- Bacterial and viral infections.
- Lactose intolerance.
- Medication.
- Psychogenic disturbances.

Treatment:

- Metronidazole which is antimicrobial drug.
- Codeine and Loperamide are anti-motility and secretory drugs.

Hirschsprung's disease or megacolon:

- Caused by absence of ganglion cells in the myenteric plexus in a segment of the colon.
- Results in constriction of the aganglionic segment of the colon.
- There is dilation and accumulation of intestinal contents proximal to constriction.
- Severe constipation also occurs.

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General disorders of the GIT:

Vomiting:

- Vomiting is the involuntary forceful expulsion of the contents of the stomach

Vomiting center:

- Area postrema located in the medulla is the vomiting center.

Causes of vomiting:

- Motion sickness.
- Medication.
- Food poisoning.
- Emotional stress such as fear.

Treatment:

- Dimenhydrinate an anti-histaminic drug.
- Scopolamine for motion sickness.
- Metoclopramide.